CENTERS FOR DISEASE CONTROL AND PREVENTION

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICE

Records of the Meeting Held on

February 20-21, 2002

Atlanta Marriott North Central Hotel
Atlanta, Georgia

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Meeting Attendance

Committee Members
Dr. John Modlin (Chair)
Dr. Gus Birkhead
Dr. Dennis Brooks
Dr. Jaime Deseda-Tous
Dr. Myron Levin
Dr. Paul Offit
Dr. Margaret Rennels
Dr. John Salamone
Dr. Natalie Smith
Dr. Lucy Tompkins
Dr. Bonnie Word
Dr. Richard Zimmerman

Ex Officio Members
Dr. Benedict Diniega (DOD)
Dr. Geoffrey Evans (NVICP)
Mr. Randolph Graydon (HCFA)
Dr. Carole Heilman (NIH)
Dr. Karen Midthun, FDA
Dr. Martin Myers, NVPO
Dr. Kristin Nichols, (VA)

Liaison Representatives
Dr. Jon Abramson (AAP)
Dr. Richard Clover (AAFP)
Mr. Stephan Foster (APHA)
Dr. Eric France (AAHP)
Dr. Stanley Gall (ACOG)
Dr. Samuel Katz (IDSA)
Dr. Martin Mahoney (AAFP)
Dr. Victor Marchessault (CNACI)
Dr. Paul McKinney (ATPM)
Dr. Kathy Neuzil (ACP)
Dr. Georges Peter (NVAC)
Dr. Gary Overturf(AAP)
Dr. Kevin Reilly (PhARMA)
Dr. David Salisbury (DPH, London)
Dr. William Schaffner (AHA)
Dr. Jane Siegel, (HICPAC)
H. David Wilson (AMA)
Dr. Richard Zimmerman (AAFP)

Office of the Director
Dr. Harold Margolis
Ms. Karina Rapposelli
Dr. Dixie E. Snider, Jr.

Office of General Counsel
Kevin Malone

MASO
Jo Jones
Helen Kuykendall
Cathy Ramadei

Epidemiology Program Office
Linda McKibben

National Center for Infectious Diseases
David Ashford
Lynn Brammer
Joseph Breese
Carolyn Bridges
Maria Cano
Marty Cetron
David Cho
Nancy Cox
Roz Dewart
Debora Dotson
Lori Evans
Keiji Fukuda
Roger Glass
Rita Helfund
Vincent Hsu
Boaming Jiang
Rima Khabbaz
Jim LeDuc
Xiuhua Lu
Migharl Maer
Brian Mahy
Allison Mawle
Ann Moen

NCID - continued

Martin Meltzer
Alicia Postema
Don Sharp
Kanta Subbarao
Jay Watson
Lisa Wld
Tim Uyeki

National Immunization Program

Ali Abdel-Moniem
Lorraine Alexander
Curtis Allen
Roger Bernier
Kris Bisgard
Carolyn Bochina
Scott Campbell
Christie Casey
Bob Chen
Susan Chu
Gary Coil
Margaret Cortese
Christine Curtis
Bacary Draminfal
Laura Erhart
Gary Euler
Katie Fullerton
Edith Gary
Jerilyn Gilbert
Beth Hibbs
Penina Haber
Steve Hadler
Marika Iwane
Alison Johnson
Laurie Johnson
Dewa Joseph
Sharon Katz
Vanda Kelly
Kim Lane
Charles LeBaron
Brent Lee
Peng-jun Lu
Dean Mason
Mehran Massoudi
Mary McCauley
Christy McKinney
Mike Monril
Gina Mootrey
Trudy V. Murphy
Tippavan Nagachita
Mary Nguyen
Barbara Newhouse
Glen Nowak
Dianne Ochoa
Dennis O'Mara
John Moran
Walter Orenstein
Ismael Oretega-Sanchez
Paba Palihaardana
Brian Pascual
robert Perry
Robert Pless
Kelly Plott
Larry Pickering
Jean Popiak
Maria Rayul
Rebecca Prevots
Susan Reef
Lance Rodewald
Jeanne Santolli
Judy Schmidt
Susan Scheinman
Ben Schwartz
Jane Seward
David Shay
Kristine Sheedy
Jim Singleton
Vishnu-Priya Sneller
Bob Snyder
Shannon Stokley
Peter Strebel
Ray Strikas
Pamel Srivastava
Charlis Thompson
Bruce Tierney
Typratap Tiwart
Diane Urban

NIP - continued

Gary Urquhart
Kim Waggoner
Fran Walker
Lin Watson
Craig Wilkins
Donna L. Weaver
Bruce Weniger
Melinda Wharton
Bayo Willis
Skip Wolfe
Laura Zimmerman

NIOSH
Scott Diechman
Richard Ehrenberg

National Vaccine Program Office
Steven Sepe
Greg Wallace

Public Health Practice Program Office
Mary Lerchen

Food and Drug Administration
Norman Baylor
Phil Krause

National Institutes of Health
Albert Kapikian
David Morens
Barbara Mulach
Lone Simonsen

Others Present
Debbie Adams, Georgia Department of Human Resources
Bascom F. Anthony, Biologics Consulting Group
Lynn Bahta, Minnesota Department of Health
Lakesh Bhattacher y ya, USP
Katherine Bryant, Georgia Division of Public Health
Joseph Beaver, TN Department of Public Health
Bryan Bechtel, Infectious Disease News
Pat Cannon, Wyeth
Dan Casto, Merck
Kathleen Coelingh, Aviron
Lenone Cooney, Cooney Waters
Dack Dalrymple, Bailey and Dalrymple
Lisa Davis, Texas Department of Health
Michael Decker, Aventis Pasteur
Carmen Deseda, San Juan, PR
Elizabeth DeSouza, Glaxo, Smith-Kline
Natalie deVane, Wyeth Lederle
Richard Dinovitz, Wyeth Lederle
Greg Dotson, Glaxo, SmithKline
David Fedson, Aventis Pasteur
Julie Fletcher, Georgia Division of Public Health
Neil Formica, CSL Vaccines
Betsy Frazer, AQAF
Dianea Gaskins, GA Immunization Program
Bruce Gellin, Vanderbilt University
Jayne Gilbert, Chiron Corp.
Ruth Gilmore, Georgia Immunization Program

E. Goodman, Stone Mountain, Georgia
Eric Greenbaum, Merck
Jesse Greene, SC Department of Health
Tamar Halpern, Buffalo, New York
Neal Halsey, Johns Hopkins Univ.
Claire Hannan, ASTHO
Kim Haupt, Merck
Rick Haupt, Aventis Pasteur
Bill Hausdorff, Wyeth-Lederle
Penny Heaton, Merck
Kathy Heidish, East Metro Health District, Georgia
Charles Helms, Univeristy of Iowa
Tami Holder di Piazza, Ketchum
J. Horton, Georgia Immunization Program
Gary Horwith, Nabi
Philip Hosbach, Aventis Pasteur
Barbara Howe, Glaxo, Smith Kline
Malcolm Hower, Wyeth Vaccines
Mike Hudgins, Alabama Department of Public Health
Dominick A. Iacuzio, Roche Labortories
Melanie Jackson, Georgia Department of Health
Andrea Krull, USAF
Edgar Ledbetter, San Antonio, Texas
Scott Litherland, Parallax Communications
Harold Lupton
Grace Maguire, Wyeth
Michelle Mattilin, Aventis Pasteur
Liz McKee Anderson, Wyeth Lederle
Marilyn McKenna, Atlanta Journal Constitution
Nestor Molfino, Baxter
Robert Myers, BioPort Corp.
Angeline Nanni, Baxter Vaccines
John Neal, Glaxo-Smith Kline
David Neuman, National Coalition for Adult Immunization
Karen Nielsen, Glaxo SmithKline
Peter Oyloe, Merck
Laszlo Palkonyay, Health Canada
Peter Paradiso, Wyeth Lederle
Nicole Pardue, Aventis Pasteur
Cindy Phillips, NACCHO
Stanley Plotkin, Aventis Pasteur
Nicki Posik, NPS
Jill Pulley, Aviron
Jane Quinn, Glaxo, Smith Kline

Zeil Rosenberg, Becton Dickinson
Michele Schimmel, Cohne and Wolfe
Kirit Shah, Aventis Pasteur
Pantaj Shere, Altanta, Goergia
Judith Shindman, Aventis Pasteur
Alan Sievert, East Metro Health District Georgia
Ben Sloat, Goergia Division of Public Health
Parker Smith, IMN
Toscha Stanely, NPS
Ron Stern, Wyeth-Lederle
Kathleen Stratton, Institute of Medicine (IOM)
Stacy Stuerke, Merck
Ben Sloat, Altanta, Georgia
Salley Somerfeldth, Nashville, Tennessee
Loch Sturrock, NPS
Dirk Teuwen, Aventis Pasteur
Jerri Ann Thatcher
Eric Tischler, Aventis Pasteur
Karen Townsend, Georgia Chapter AAP
John Trizzino, Henry Schein Inc.
Ted Tsai, Wyeth Pharmaceuticals
Miriam Tucker, Pediatric News
Eileen Undercoffler, Merck
Peter Vigliarolo, Cooney Waters
Richard Ward, Children's Hopsital, Cincinnati
Tom Wayter, BioPort Corp.
Deborah Wexler, Immunization Action Coalition
Steve Yelle, Glaxo SmithKline
Greg Yoder, Peachtree City, GA
Laura J. York, WLV
John Zahradnik, Aventis Pasteur
Thomas Zink, Glaxo, Smith Kline
Paul Zuydhbek, PLHBH, Buffalo, NY

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
DRAFT MINUTES OF THE MEETING

February 20-21, 2002

FEBRUARY 20, 2002

Opening Comments/Disclosures
Dr. John Modlin, Chair of the Advisory Committee for Immunization Practices (ACIP), convened the meeting at 8:30 a.m. He asked the members, in introducing themselves, to provide any statements of financial conflict of interest. With such a statement, they may still participate in all discussions, but may not vote on any issue related to that conflict, nor may they introduce or second resolutions pertaining to the Vaccines for Children (VFC) program.

Attendance
The members, liaisons, ex-officio representatives, agency and support staff, and interested members of the public in attendance are listed in the preceding pages. Those reporting potential conflicts were:

- Dr. Rennels: conducted vaccine trials with Wyeth, Lederle, Merck, Glaxo Smith-Kline and Aventis Pasteur.
- Dr. Paul Offit: is co-holder of a patent on a bovine-reassortant rotavirus rotavirus vaccine and consults on its development with Merck & Company.
- Dr. Myron Levin: conducts research with Merck and with Glaxo Smith-Kline.
- Dr. Richard Clover: Potential conflicts of interest with Wyeth Lederle, Glaxo Smith-Kline, Merck, Pfizer and Bayer.

Committee Business
Executive Secretary's Report. Dr. Snider made several announcements

- He welcomed several new ACIP members:
  - Member Robert B. Belshe, M.D., Saint Louis University Health Sciences Center
  - Member Guthrie S. Birkhead, M.D., M.P.H., New York State Department of Health
  - Member Celine I. Hanson, M.D., Texas Department of Health
  - Member John B. Salamone, National Italian American Foundation (NIAF)
  - Liaison David A. Neumann, Ph.D., National Coalition for Adult Immunization
- He reported a review of the ACIP policies/procedures by the Office of Government Ethics, DHHS and CDC staff, and resulting planned changes to the conflict of interest waiver letters that are issued for members on occasion.
- The ACIP addresses are www://cdc.gov/acip ; e-mail: acip@cdc.gov
- The next ACIP meetings will be on June 19-20 and October 16-17 at the Marriott Century Center Hotel in Atlanta, Georgia.
- He urged the members to maintain the necessary meeting quorum of eight members.
- The charter authorizes the Executive Secretary or designee to temporarily designate ex-officio representatives to vote, when less than eight appointed members are qualified to vote due to the lack of a quorum of members without financial conflict of interest. The

ex-officio representatives are requested to vote and to disclose any potential conflicts of interest.

Chair's Report. Dr. Modlin also welcomed the new members and drew the members' attention to the updates and informational pieces in the meeting books: the published ACIP General Recommendations, updates on the anthrax vaccine and pneumococcal conjugate vaccine shortages. He requested that comments on a distributed draft statement to change the rabies recommendation be sent to Dr. Charles Rupprecht by March 1.

Yellow Fever Vaccine

Dr. Clover introduced the draft statement on yellow fever developed by the Yellow Fever Workgroup, which was a subset of the Adult Immunizations Workgroup. He summarized several of the changes, which included a name title change related to the adverse effects of vaccination; incidence rates; and revision of the statement about testing after vaccination in some populations, especially among pregnant women, and the rationale for that revision.

Dr. Marty Cetron thanked Dr. Tony Marfin and his colleagues at Fort Collins and the working group who assisted development of this document. In its work on multi system organ failure, the end stage of yellow fever disease, the Yellow Fever Workgroup concluded that yellow fever represents clinical spectrum of disease. Some more moderate manifestations have only specific organ involvement (especially liver and kidney), which can allow recovery.

Outcome definition. The outcome of interest was named in this document as Yellow Fever Vaccine-associated Viscerotropic Disease. Yellow fever virus can be a viscerotropic disease (wild-type or the more moderate manifestation) or a neurotropic one (with identified effects include postvaccinial encephalitis). The largest clinical trial (Monath et al) to date of yellow fever vaccine compared the yellow fever YF-Vax® vaccine with the United Kingdom's Arilvax.® Active monitoring for adverse effects was done up to 30 days postvaccination. The frequency of elicited adverse events was higher than those passively reported to VAERS, with ~15% in both groups reporting fever. But 3-4% of recipients also had mild asymptomatic elevated liver enzymes which returned to normal levels by day 30. While the study was too small to detect rare events, it was significant to note that the occurrence of transaminase events suggested some replication among the vaccinees.

Incidence. To crudely estimate yellow fever incidence in areas of at best passive or non-existent surveillance, the workgroup used reports of distributed yellow fever vaccine doses. There were no data on the completeness of utilization of all the lots distributed (e.g., some vaccinees in the Brazilian vaccination campaigns received multiple doses and others received none). To date, this syndrome has been seen only in primary vaccinees, not in those with previous immunity or secondary boosters. The normal viremia also seen to 7 days post-vaccination is also absent in people receiving a booster dose. Since it is suspected that the pathogenesis of the viremia is the vaccine strain, followed by viral replication and target organ damage, it was not surprising that previously vaccinated persons would not have the viremia or target organ damage.
While the incidence rate is unknown, the theory that the frequency is not high and could be quite

rare was supported by Canada's review of its VAERS equivalent data. Martin et al's VAERS data review (*EID*, December 2001) indicated ~1.5 million doses distributed by manufacturers in the United States to primary vaccine recipients from 1995-98. That resulted in 2.5 cases per million doses, most of which were delivered in single dose vials. Brazilian campaign reports reflect two published cases out of ~23 million doses, although other suspect cases were also reported. Those data produce a crude estimated incidence of .09 cases/million doses, and therefore an overall incidence range from 0.9-2.5.

Vaccine use in pregnancy and among those with altered immune states produces a diminished response. The use of a neutralizing antibody test to assess the take in those populations in the U.S. is desirable, but the assay is limited in availability (at CDC and 1-2 academic settings). Therefore, the statement recommends consultation with CDC and the Ft. Collins laboratory staff to determine the timing and ability to do that test prior to the person's travel departure.

Basically, the recommendation makes no change to the 1993 statement on the vaccine's indications: persons traveling or expatriates living in areas were yellow fever virus transmission is endemic or epidemic should be vaccinated, with the recognition that rare viscerotropic events can occur. The vaccine is underutilized by persons going to such areas, so a few cases have been imported by Americans traveling to the underdeveloped world. The statement urges that the vaccine be used by those at risk rather than over- or under-utilizing it.

Discussion included:

- *Are there data on immunogenicity in pregnant women from the second and third trimester?* These data are from developing country settings and are confounded by malnutrition, an important point. The proportion of women immunized during pregnancy with a positive response was lower than the 90-95% reasonably expected. Of the 81 pregnant women immunized and followed, one had a congenital anomaly that could have been a vaccine-type virus, but they were not linked. This is a small data set.
- *Were there any data on the concomitant use of malaria prophylaxes such as methloquin?* Not that specifically, but there was no significant interference to protection from similar preventive prophylaxis of chloroquin.
- *Are there data on take in symptomatic- versus asymptomatic HIV patients, and what the role is of viral load, CD-4, prescribed heart medication, etc.? It may be worth considering that a patient under the care of an HIV-experience physician, with suppressed viral load and an adequate count, could be sufficiently immunocompetent to respond to the vaccine.* That was discussed in the recent literature, which proposed an arbitrary CD-4 count of 200 as the cut point and advised caution for lower counts, but the data are insufficient to clearly define such a point. Data on symptomatic versus asymptomatic patients indicated a safety profile for both manifestations, but the study's inability to cite a specific reference for that prevented making that statement in this document.
- *How was the use of 10 milligrams of prednisone arrived at, rather than 20 milligrams cited in other documents?* Two milligrams per kilo, to a maximum of 20 milligrams, was derived in the past based on some data indicating the possible suppression of delayed

immune response, but the data were soft and arbitrary. Consistency is preferable, but with the presence of recognized although rare complications in presumably normal hosts, even the possibility of increased risk among the immunocompromised must be considered.

- *The rationale to not vaccinate those aged <4 months of age is provided, but there are no data to help the physician judge the risk of giving it to children aged 4-9 months.* The variability of settings of the vaccine studies presented a challenge to that determination. Six-month-old children are safely immunized in the Amazon. But in the early trials of the 1940s, the post-vaccinial encephalitis or neurotropic profile occurred most frequently in those aged <6 months, and some cases occurred in those aged 4-9 months. The attack rate can be up to 30% in an outbreak area, and the risks are quite variable; outbreaks can be seasonal or sporadic and areas can be endemic and epizootic. Optimally, the vaccine should not be given at <9 months, but babies have been safely vaccinated at age 4-9 months in endemic areas in Africa and South America.
- *Before the phrase "17 B vaccine strain," insert "To concentrated preparations of...".* (Dr. Decker, of Aventis Pasteur, referencing the page 4, line 115 indication for lab personnel). Agreed; primary contact with vaccine strain virus was the intended focus, not remote secondary contact.
- *Add "estimates prevented previously, but actual incidence is likely to be higher" to the line 315 (range of reported frequency of 0.09-2.5/1 million doses). This is based on VAERS passive surveillance, which involves under-reporting, as shown in rotavirus and intussusception.* Dr. Chen reported that the Workgroup is developing an estimate of how much higher that should be. For the moment the term "higher" will be sufficient; there is no need to quantify the current imprecision, in view of the variability in reporting efficiency.
- *Add text to the document regarding: 1) research gaps; 2) simultaneous vaccination with other vaccinees such as methloquin;*
- The international health regulations requiring boosters every ten years are developed by the WHO and are adopted by countries either in whole or in part. Revisions are infrequent. The recommendation for a ten-year booster focuses more on the needs of developing nations than on the U.S. experience.
- The need for a special yellow fever vaccination certification stems from large outbreaks that occurred during resettlement in colonization to avoid importation into the home country. With urbanization occurring in such areas as Latin America, it was left in place, and Asian countries will not admit people without that certification.
- *The disease is clearly systemic in all cases, but multiple organ failure occurs in key, but not all, cases. Studies suggesting that the vaccine virus is viscerotropic are compelling but not proven in other cases in the U.S. due to lack of samples for analysis. Why not call this "vaccine-associated yellow fever (viscero- and neurotropic)?*. This was discussed. The term "association" was chosen to indicate causality, but also suggests that this is not yet proven. While the "viscero" indicates the vaccine caused it, something certain in the Brazilian cases, that is only one possibility in the U.S. cases. A simple term is needed now, but as more cases are identified, more definition will be possible. Dr. Midthun suggested calling it, therefore, "vaccine-associated organ system disease."

Dr. Clover summarized the suggested changes: 1) line 93-95, change the prednisone dose to 20 mg; 2) line 115: insert "concentrated preparations of" before 17-D vaccine; 3) line 315: add "However the true incidence may be higher"; 4) add a paragraph on the research gaps.

Dr. Zimmerman moved to adopt the amended statement, and Dr. Levin seconded the motion.

Conflicts: Aventis Pasteur
Vote:
In favor: Smith, Zimmerman, Tompkins, Salamone, Deseda, Brooks, Offit, Levin, Birkhead, Word, Modlin
Opposed: None
Abstained: Rennels
The vote passed.

Informational Update/Anthrax Recommendation
NAS Meeting. Dr. Charles Helms summarized some of the activity to address the use of anthrax vaccine, since the ACIP's last recommendations were forwarded to CDC Director Dr. Koplan. A December 2001 meeting was held at the National Academy of Sciences to discuss optimizing the post-exposure prophylaxis (PEP) administration and to assess the sufficiency of the initial recommendation. The precipitating event for this review was the response to the contamination of the Hart Senate office building, which produced higher-than-expected spore concentrations.

Specifically at question, in view of the high spore inoculum, was the adequacy of the 60-day antibiotic PEP recommendation, versus a protocol coupling that with anthrax immunization and a longer treatment period. Scientific papers were presented, much of which had been reviewed by the ACIP during its initial recommendation and advisories to Dr. Koplan in late 2001. Since then, epidemiologic investigations suggested that the anthrax exposures may have been higher than those used in animal model studies, prompting question of the prophylaxis protocol. In addition, a study of 9000 persons with suspected anthrax exposure who were on the 30-day PEP revealed a wide range of protocol compliance. And finally, more anthrax vaccine (AVA) was licensed and therefore available for civilian use, but the AVA was not licensed for post-exposure prevention of anthrax.

The ACIP endorsed the use of the drug as an IND among exposed persons, to the concurrence of the Johns Hopkins Center for Civilian Biodefense Defense Strategies. However, the states were less enthused, due to the controversy over determining who was at greatest risk, whether the vaccine was necessary, and the opinion that those outside the Hart setting were unlikely to take the vaccine. The anthrax vaccine was released as an IND, coupled with a 30-day antibiotic PEP. Media accounts indicate low demand for the vaccine.

CDC Activity. Dr. David Ashford, DVM, MPH, DSc, of the Meningitis and Special Pathogens Branch of CDC's National Center for Infectious Diseases, updated the committee on the details of CDC response to the *b. anthracis* attack, use of vaccine in PEP, and new information

pertaining to the original recommendations. He thanked Dr. Helms for his work over two years on the anthrax recommendations and regretted his departure from the Workgroup on Bioterrorism Awareness.

The ACIP had discussed anthrax vaccine on several occasions: October 1999 (discussed anthrax and vaccination recommendations); February 2000 (reviewed the science regarding vaccination and PEP); and June 2000 (issued recommendation of vaccine use as an IND).

Dr. Ashford outlined the initial case in Florida of inhalational anthrax. The patient died and the inhalational infection was confirmed by autopsy on October 6. On October 12, a cutaneous case in New York City led to investigation and discovery of other cases in New Jersey, Washington, D.C., and Connecticut by November 20. The final inhalational of November 14 was never identified for delivery mechanism, but the other cases were associated with letters postmarked September 18 and October 9.

An IND application was filed with the FDA to use anthrax vaccine for PEP and the ACIP reconvened and endorsed a routine use of 60 days of antibiotics for PEP. This was a modification from the original discussion of the 30-60 day range, which was felt to be too difficult for practical application by physicians. About 10,000 persons were advised to take 60 days of antibiotic therapy, from October 8 to November to 25, mostly due to occupational exposures to personnel in the media, postal workers, and Capitol Hill staff.

A complicating factor for prophylaxis is that the spores remain in the lung for long periods. The Henderson 1956 study of macaques exposed to an estimated 400,000 anthrax spores retained 65% of the spores in the lungs for 15 days, 15-20% for 42 days, 2% for 50 days, and traces were detectable even to 100 days. Some human data from the Sverdlosk accident also indicates possible extension of the incubation period in humans out to 43 days. Those data raised additional concern about the potential need for added PEP.

Additional considerations relevant to the vaccine included:

- *Risk assessment of the anthrax threat*. The Defense Research Establishment Suffield (DRES), Canada's equivalent to the **U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID)** studied weapons-grade *B. globigii* spores from February through April 2001 to simulate an envelope release of *B. anthracis* in to an office-sized room (18'x10'x10'). Sophisticated aerosol sampling estimated 480-3,080 LD50s in a 10-minute exposure, compared to the 8-20 LD50s seen in the macaque studies.
- *Risk of reaerosolization after primary release*. These risks were considered negligible from discussions with the Department of Defense (DOD), but their experiences were gathered in different environments than seen in these attacks. Some preliminary data generated during the response suggested that reaerosolization is a concern.
- *PEP adherence:* Initial data indicated adherence ranging from 40%-98% for the 60-day antibiotic treatment advised.

- The IND Protocol for PEP remains in effect for all those known to be exposed to *B. anthracis*: informed consent for adults; three subcutaneous anthrax injections at 0,2,4 weeks; and 40 additional days of antibiotics (ciprofloxacin, doxycyclin, or amoxicillin). The protocol for children is three intramuscular vaccine doses over the same period, with 40 additional days of antibiotics (ciprofloxacin, doxycyclin, and a switch to amoxicillin when susceptibility results are known).
- *Results:* Currently (as of February 20, 2002), the PEP IND has been implemented at all affected sites. About 5,400 individuals were educated about PEP and 1740 enrolled (32%); 1548 received antibiotic only and 192 received antibiotic and vaccine. One serious adverse effect of acute renal failure was reported in a person who received ciprofloxacin but not vaccine.

Discussion included:

- *Dr. Stan Plotkin was not surprised at the lack of confidence in the vaccine, despite recommendations from two expert committees, because the consent form was so written that he himself might not have taken the vaccine. He advised discussion of the risks and benefits and a review of the form.* The generation of the form was an unprecedented activity, done by CDC with multiple reviews by a high-level staff of the FDA, the Office of Human Research Protection, DHHS, and a White House staffer. CDC's Deputy Director of Science, Dr. John Livengood, led those discussions. Given the time pressures, level of involvement, and points of view, Dr. Livengood was complimented on getting the work done. CDC hopes that, as a smallpox vaccine consent form is developed, other options can be explored to avoid such a compressed time frame.
- More discussion is needed on use of this vaccine in children.
- *If there is another highly concentrated contamination event, would the move to vaccination be faster? And should pre-exposure vaccination be done for such personnel as laboratorians?* There are now ~220,000 doses available, enough PEP for 73,000 people. The recommendations on using vaccine in combination with antibiotics will stand. Although the FDA considers the vaccine safe and efficacious, the largest supply now available is not licensed, and there is a limited supply of doses of the licensed vaccine. There is some disagreement about deploying licensed doses for preexposure prophylaxis or retaining them in case of a greater public health emergency. There is hope of resolving this in further discussions or through more vaccine supplied through negotiations with DOD and increased production by BioPort.
- *Why was a cutaneous rather than intramuscular injection selected?* Though preliminary data from a pilot study conducted by DOD has indicated lower reactogenicity with intramuscular injection, the vaccine is licensed for subcutaneous injection. Intramuscular injection of both adults and children was discussed with the FDA. Opinions differed, but the consensus was reached on the subcutaneous route.
- *What education will be needed if the vaccine needs to be used again?* Ongoing communications are improving the public's knowledge about this vaccine. The importance of education was one reason that CDC insisted that its own staff do the educational presentation, rather than postal officials, corporate executives, etc.
- *Will a licensure for PEP ever be possible to avoid IND status for the anthrax or smallpox*

vaccines? The human data for that could never be collected; this IND was released since the product itself was not licensed and was being used for an indication the vaccine itself did not have. However, Dr. Midthun reported FDA's "animal rule," soon to be finalized, that would allow indications for some products to be used based on animal data demonstrating efficacy in a post-exposure setting.

Influenza Vaccine

Chair Dr. Bonnie Word introduced the activity of the Influenza Workgroup since the last meeting and outlined the presentations to be provided. Key issues discussed included providing the vaccine to healthy children, implementation of this new pediatric immunization, effect on the VFC program, economic considerations, the 2002 recommendations, and thimerosal issues. She noted that in future, the new influenza vaccine recommendations would be discussed and approved in the October rather than the February meeting.

Influenza Surveillance/Strain Selection. Ms. Lynette Brammer reported on the light to moderate influenza virus circulation in the current season activity and the vaccine strain a selection for the next season.

- Patient visits to sentinel physicians peaked later than the previous two years. The 122 Cities reporting system indicated that mortality has not yet exceeded the epidemic range.
- Worldwide, A (H3N2) viruses have predominated, while A H1 has been rare; B has been less commonly identified, but has dominated in some European cities. There are two B lineages: B/Victoria and B/Yamagata (the lineage contained in the vaccine). The Victoria strain has circulated only in Asia since 1991, but is spreading out to North American, Europe and the U.S. Most of Canada's strains have been from the Victoria lineage.
- A new influenza virus, A (H1N2) has been detected in Asia, Africa, Europe, and North America. It is a reassortant of the currently circulating influenza A (H1N1) and A (H3N2) subtypes. Vaccine coverage of H1N2 viruses should be good, since A (H1N1) and A (H3N2) both are in the current vaccine.
- FDA retained the A/New Caledonia/20/99-like H1N1 strain component, and the A/Moscow/10/99-like (H3N2) strain and will meet in March to finalize the strain selection used in U.S. vaccine. WHO met in February and retained the current H1N1 and H3N2 components, but updated the B component to a B/Hong Kong 330/2001-like virus (from the B/Victoria lineage). The H5N1 virus was isolated in Hong Kong chickens in 2002, many of which were slaughtered, but no human cases have been reported.

2001 Influenza Vaccine Supply Mr. Dennis O'Mara, NIP's Associate Director of Adult Immunization, updated the committee on the 2001 supply. Based on July 2001 population estimates, influenza vaccine was delivered to 74 million high-risk adults, 7 million health-care workers, and 17 million individuals in the target population (healthy adults aged 50-64 and household contacts aged <50). Influenza vaccine production was 77.2 million doses, 77.9 million doses, and 87.7 million doses in 1999, 2000, and 2001, respectively. In 2001, the distribution by October greatly surpassed that period in 2000; by the end of November, it almost equaled the 1999 distribution. But subsequent difficulties occurred, including a distribution

delay, and it is too soon to know the impact on coverage. National Health Interview Survey (NHIS) data indicate that from 1997-2001, of those aged 18-49 , 20% were covered; as were 30-38% of those aged 50-64 and 63% of those aged 65 (possibly due to distribution delays). About 88-93 million doses of influenza vaccine are projected by the manufacturers to be produced for this coming season.

Update on Feasibility Study of Influenza Vaccine for Pediatric Use. Dr. Marika Iwane reported on a set of studies of the feasibility of influenza vaccine for pediatric use, done in collaboration with University of Rochester. This was studied in focus groups with primary care providers and in surveys of pediatricians and family physicians. A time and motion study of Rochester-area practitioners was also conducted, as well as a study of a database which included 70% of Rochester area children.

National Influenza Vaccination Survey. Mailed to pediatricians and family physicians in February 2001, this survey explained that studies show children at high risk for influenza. It notified them that the ACIP, AAP, AAFP, and others were considering recommending universal influenza vaccination for all children aged 12-35 months of age, either nasally or by injection. The response rate was 58%. Survey responses were as follows:

- Feasibility in the practice: 76% agreed, 17% disagreed or were neutral.
- Agreement to the overall policy: 58% agreed, 22% disagreed or were neutral.
- Opinion that adding influenza vaccine would deter/delay other vaccines: 66% disagreed, 20% were neutral.
- Barriers identified: 1) vaccine cost; 2) inability to identified children to be vaccinated. Family physicians specifically cited costs to the family and a crowded vaccination schedule.
- Implementation method: during well child visits (most), during an illness or follow-up visit, or a vaccination only visit. Most preferred to vaccinate in their own practice.
- Feasibility to vaccinate 12-35 month-olds with only injectable vaccine available: nearly impossible: 8%; much more difficult: 45%; slightly more difficult: 38%. Implementation feasibility was thought better among 6-12 month-olds.
- Family physicians were more likely to oppose universal vaccination and report barriers. Opposition was based on: influenza perceived as not serious enough, could delay other vaccinations, parental objection, and if only injectable vaccine was available.

Time/motion study. This measured the time spent by practices in delivering influenza shots, from December 2001 to January 2002 in seven primary care practices in Rochester. Analysis indicated:

- Times reported were twice as long and urban versus suburban practices.
- Actual vaccinations required ~.1.5-2.3 minutes; 80-90% of the patients' time was spent waiting.
- A nurse practitioner or physicians examined the patients in only 10% of visits.
- Overall median time spent on the vaccination process was 16 minutes.
- Median exam room time: 10 minutes
- At 6 patients/hour per room, a range of 29-104 patients could be seen per 8-hour day.

- 100 children requiring influenza vaccination would require: 16 hours (4 half-days) of examination room time, 12 hours of additional staff nurse time, and 10 minutes of physician or nurse practitioner time.

The *insurance database analysis* is still analyzing the data for different scenarios. The initial analysis estimated the additional visits needed for universal vaccination of children aged 6-23 months (likely to be targeted to the recommendation) during an influenza vaccination season. Data on ~42,000 children of that age range in six Rochester-area counties was analyzed. Most (76%) children were seen in pediatric practices, 11% in family practices, and the balance in hospitals and neighborhood health centers. Selected results of the analysis include:

- Using all well-child care (WCC) visits for influenza vaccinations: 38% of children would need one additional visit, 33% would need two additional visits.
- If all visits are considered as opportunities and never missed, and only WCC visits are considered, 33% need one more visit; 146% would need two.
- Providing shots/nasal influenza vaccine at any visit required less extra visits.
- Little variation between urban, suburban, and rural children, or among practice types; only age posed any variations.
- Study implications: with 100 patients requiring vaccination, using all visit opportunities, 33 would need one more visit, 13 would need to more visits, to total ~60 extra visits. Holding vaccination clinic hours could reduce the burden. The estimates did not include pulling and filing charts or reminder/recall.
- Conclusions: Most physicians thought universal recommendation was feasible: substantial extra visits would be required: vaccination clinics could reduce the burden: educational activities may increase the recommendations acceptance.

Discussion included:

- *Were visits saved due to the vaccination calculated?* Not as yet.
- *Was the time spent discussing risks and benefits included in the time and motion study*? The administrative component of two minutes included explaining, preparing, administering, cleaning up, and appeasing the patient. Dr. France noted that time and motion studies in general show that physicians spend 30 seconds, if that, explaining vaccines. Families generally read the vaccine information sheet (VIS) while waiting, and are asked if they read it and have any questions.
- *Did the survey cover sheet make any assumptions about coverage for the vaccine (live attenuated or inactivated) or visit costs?* Only a very general statement indicated that insurance and VFC were expected to cover these costs in the same manner as other childhood vaccines recommended by the ACIP.
- *Was it investigated why practitioners were more negative about delivering immunizations in public health or day care settings?* No.

Economics of Routinely Vaccinating Children Aged <5 Years Against Influenza. Drs. Martin Meltzer and Kathy Neuzil presented the results of analyses of data drawn from two published studies. The data of the Tennessee Medicaid data set covered children aged <15 years over 19 consecutive influenza seasons, from 1974-1993. The study assumed a baseline rate of acute

respiratory events, with an increase of acute respiratory disease and hospitalizations in the winter season, which was defined as the respiratory syncytial virus (RSV) season. The study looked at the degree of excess disease during influenza circulation versus RSV season for the outcomes of hospitalizations and deaths from pneumonia, influenza, as well as a broader range of acute cardiopulmonary conditions and outpatient visits.

The variable benefits not included in the economic model included: predictable health-care utilization for vaccination versus the unpredictability of illness extent during the season/disease; effect on practice and on antibiotic use; effect on household transmission; and preparation for pandemics. The risks not considered included new adverse effects that may be non-causal or rare; feasibility issues of supply and delivery, few data on coadministration with other vaccines, and the thimerosal issues.

A Monte Carlo economic model was used, which builds in a season-to-season variability rather than assuming a consistent outcome rate. The age groups analyzed ranged from 6-<24 months, high- and non-high risk, and data were presented in cohorts of 1000 per age- and risk-group. The data sources and assumptions involved the rate of outcomes, three attack rate ranges (10-20%, 20-30%, and 30-40% to allow for a percentage of children who do not visit a physician for influenza but stay at home); and the rate of otitis media caused by influenza.

Hospitalization rates per 1000 for those aged 6 months to ≤24 months were estimated for the non-high and high-risk groups. Since the variation of influenza year-to-year makes a single number impossible to relate the changes in hospitalization rates, the frequency of the actual data was charted and then superimposed on a mathematically calculated distribution curve. The mean of the actual data and fitted distributions shown on a curve was 2.2/1000 with a standard deviation of 3.6, indicating that the variability of itself is larger than the mean, and that the mean hides more information than it reveals about the hospitalization risk of a non-high risk child aged 6-24 months.

The costs considered included the costs of vaccination (vaccine, administration, parent time off work, travel, side effects, two doses at first vaccination); productivity costs (value of a work day); and health outcomes (death, hospitalization, outpatient care, ill but not requiring medical care). Vaccine effectiveness is not equal from year to year. It is ≤52% effective 10% of the time, and it is rare for mass vaccination vaccine to be >90% effective. Most literature suggest that the mean, median, and mode occur between the 70-77 percentiles.

The results of net returns per 1000 for those not at high risk, counting all costs and savings, were:

- 6-24 months: Break-even threshold value (no gain or loss to society) at a total vaccination cost of $30.
- 6 months to 5 years and 5-15 years: Mass immunization of non-high risk groups will not generate a net savings at $30.
- It is unknown how costs will change as mass vaccination increases. Some believe that a nasally-administered live attenuated will be less expensive when mass-distributed in

clinics, but a new vaccine also will likely be more expensive than the current one.

- High-risk children involves a different scale of economic returns; the returns are consistently >0. Between a $20-40 vaccination cost, vaccination of high-risk children is more likely to offer savings to society than vaccinating those not at high risk.
- The probability and impact of death due to influenza, although a very rare event, is very important in an on economic analysis. Death is the single most important variable, not the probability of going to the hospital. With increasing risk, the threshold of increasing breakeven value rises as well.

The study's overall conclusions were:

- There is a large variability in the rates of health outcomes. Mass immunization will not prevent a fixed number of outcomes per year, since influenza changes from year-to-year.
- The most important inputs to this model's net present value were the rates of death and outpatient visits and the costs of vaccination itself. Others provided much less impact.
- The majority of savings (67%) were indirect (parental time not taken off from work), even when death outcomes were excluded. This is significant since it infers that the health care system (the payers) will not benefit the most from this recommendation, begging the questions of who pays and who benefits.
- Consistent savings also are unlikely from vaccinating non-high risk children unless the vaccination costs <$20/child. Is almost always more cost efficient to vaccinate high-risk populations.
- To vaccinate the non-high risk children plus 10% of the high-risk population requires a threshold cost of $37 per child.

Discussion included:

- *How big a benefit economically is the indication of ongoing studies of the prevention of collateral infections in those vaccinating?* Prevention of onward transmission to other household members may provide large savings, but the valuation of the savings might be very different; many will not vaccinate a child to prevent transmission to adults. Even considering children aged<2 years, whose influence on a household may be larger than that of older children, this was listed as an intangible for that reason.
- *The inability to quantify and place a value on human suffering is a problem, although there certainly is a value to preventing several days of high fever and intense coughing.* There are some new methods that may approach those values, but the valuation might be transient over time. While vaccinating the 5th percentile does not save money, it is not moot that it should not be done; society's values may dictate that it should be done and that becomes a matter of public debate. The point of an economic analysis is to inform that debate.
- *Are the cost savings for vaccinating those age 50-64 years, already approved for vaccination, different?* No economic analysis looks at only the 50-64 year-olds, but there are studies of adults among whom prevalence and risk factors increase.
- *Did you calculate the incremental increase in benefit and cost of adding influenza vaccination on top of pneumococcal vaccination?* Those are interesting issues, but that was not incorporated because this recommendation is separate from that for

pneumococcal vaccine. Perhaps that should be revisited.

- *Have these data been analyzed separate from societal costs, such as from the health plan perspective?* Not yet, but that should be calculated by the time it is ready for publication.
- *What is the percent of U.S. children aged <2 years in the risk categories for which the vaccine will be recommended; and please address the issue of the inability to vaccinate high-risk children with a selective recommendation.* The non-high risk and 10% high-risk population was estimated by asthma prevalence (5-8%). Vaccination did not include household members as well as high-risk children, but the results suggest that, compared to those not at high risk, society could afford to pay a premium for the health care system to target and vaccinate the 10% of the children who are at high risk.
- *The costs of vaccination depend on the sensitivity analysis. What is the effect of immunizing on weekends or in nontraditional settings to lower the costs of vaccination?* Assuming $30 as the cost of taking a child for influenza vaccination outside of a well-child visit, a more convenient weekend clinic time would lower the cost. Independent studies of what the charges would be could be done.
- *Negative hospitalization rates for influenza seem counterintuitive; and from where was the $3366 estimate derived?* The negative hospitalization rate reported resulted when fewer children were hospitalized during the influenza circulation period than the periods before and afterward. All distributions showing ≤$0 were related to excess hospitalization; this did not infer any savings. The $3366 hospitalization value came from the Medicaid database of reimbursement rates to people enrolled in large health insurance plans.
- *CDC must be clear about the significant differences between the current inactivated vaccine and the cold adapted influenza vaccine under development:* The vaccine parameters in this study applied to the current inactivated vaccine used, but an economic study on the cold-adapted influenza vaccine has also been presented to some of the workgroup. That model has a threshold of $250/dose.

Implications to the VFC Program

Dr. Lance Rodewald summarized the current coverage for the children eligible for the Vaccines For Children (VFC) program whom the ACIP says "should" be vaccinated: those with chronic pulmonary or cardiovascular disorders, household members of high-risk individuals regardless of age, etc. But the VFC does not currently cover the permissive recommendation for those whom the ACIP says "may" be vaccinated. While experience has demonstrated that such permissive recommendations do not work, that may not necessarily always be true.

Providing VFC coverage for influenza vaccine poses a number of implications:

- The 45,000 VFC sites consist of 75% of physicians in private practice and 25% in public clinics.
- VFC providers vaccinate ~95% of young children when public and private vaccinations are combined, implying VFC's potential to be the leading edge for ACIP recommendations.
- VFC participation can be expanded by enrolling more providers such as specialists.
- All VFC sites serve Medicaid-enrolled, uninsured, or American Indian or Alaska Native

children. The federally qualified health center (FQHC) and rural health center (RHC) sites also serve the under-insured who do not have immunization covered in their commercial health insurance plans.

- About one-third of the childhood population under age18 receives VFC vaccine.
- Expanded VFC coverage for influenza vaccine may help promote influenza vaccination, following the precedent of pneumococcal conjugate vaccine.
- Implications for partners include a potential two-tiered system in which a child is turned away due to their insurance classification, not their medical condition; state vaccine financing or providers' health insurance coverage affecting a 2-tiered system; and logistical issues.

Next steps include:

- Promote influenza vaccination of high risk children who now have low vaccination rates. VFC coverage is already in place, implying the need for widespread provider outreach. It may be possible to use the new Section 317 infrastructure funding to state and urban area health departments; and providing such coverage is obviously important for children's health, since influenza is the primary vaccine-preventable disease killer of children.
- Determine the implications of expanded VFC coverage (e.g., acceptance by partners, estimates of vaccine needs). Discuss vaccine uptake with partner organizations, professional societies, states, etc.
- Reimbursements for providers to administer vaccines are normally based on direct costs, not societal benefits, and inadequate reimbursement is a barrier to immunization providers. If reimbursement is less to the provider, will that impact other VFC vaccine delivery such as MMR and varicella? Medicaid will pay for vaccination for the "may" as well as the "should" group. Those fees are higher in general than Medicare payments to physicians. Such issues requiring address in the proposed discussion and ACIP suggestions will be noted. But the final CMS rule on vaccine administration fees is in effect and may spill over to private industry.
- CMS conducted a study 3-5 years ago of the actual cost to vaccinate, which produced consistent information across the country despite poor participation. That study was not published; Mr. Graydon agreed to check on its status for the committee. It is possible that CMS would welcome recommendation of better support from Medicaid reimbursement. VFC also saved the Medicaid program money by paying for the vaccines, so many states rolled that savings into their administration costs. More detailed information can be presented at the June meeting.

Pediatric Influenza Vaccination Options for ACIP Recommendation

Dr. Keiji Fukuda outlined the issues that have been reviewed by the Influenza Workgroup on the impact of influenza on children, the safety of **trivalent inactivated vaccine (TIV) and live attenuated influenza vaccine (LAIV), immunogenicity and effectiveness,** economic implications, and feasibility and implementation issues.

He presented three options developed by the Workgroup for the ACIP's consideration and

recommendation:

1. No change from the current recommendation: vaccinate children aged 6-23 months with high-risk conditions.
   Advantages: Focuses attention on children with conditions placing them at high risk for complications, which may not have been sufficiently promoted in past, and raises the fewest feasibility concerns,
   Disadvantages: Despite the longstanding recommendation, vaccination coverage remains low, and this ignores the increased risk for hospitalization in young healthy children.

2. Encourage vaccination of children 6-23 months and defer the proposed recommendation for 1-3 years, adding additional language in the recommendation about vaccine safety and effectiveness.
   Advantages: Focuses attention on young children, provides "notice" of ACIP's intent, and provides a definite time frame for conducting anticipatory activities (e.g., education and data collection).
   Disadvantages: Does not focus attention on children aged 24-36 months or those with high risk conditions; will increase demand/stress on vaccine supply; and 1-3 years may not be enough time to implement all desirable preparatory activities

3. Recommend annual vaccination of children aged 6 months to ≥3 years.
   Advantages: Healthy children in this age group have significantly higher risk of flu-related hospitalization, and the upper age limit of the recommendation can be raised.
   Disadvantages: Does not focus attention on children 24-36 months of age or older children with high-risk conditions; will increases demand/stress on vaccine supply, and pediatricians and the public may be inadequately prepared for this recommendation at this time.

Discussion included:

- A universal influenza recommendation is needed. The previous recommendation focused on high-risk children and they are still not being immunized.
- The Workgroup was most comfortable with encouraging vaccination for those aged 6-23 months and beginning the educational programs with the AAP, AAFP, and using the broadcast capabilities of CDC's Office of Communications to advise the field of that intent.
- Dr. Abramson reported Dr. Rennels' work for the AAP on a policy statement to be ready for their spring meeting. It would follow Option 2, educate physicians that these children are high-risk, and then in 1-2 years issue a universal recommendation. Impediments to issuing the universal recommendation is that it could place practitioners in a medical and legal bind and the logistical issues could prevent practitioner compliance. One good study in support is published, but is not premised on the current reality. More research is needed.
- The varicella model was cited as an example of slow uptake after the 1995 recommendation, although coverage is now at 70%. Education of the physician and parents about the vaccine's value drove that. However, the uptake under Option #3 is

likely to be slow and does not have varicella's advantage of a school entry requirement.

- Dr. Martin Mahoney presented the AAFP's perspective of the logic of doing the education first, particularly since coverage in high-risk groups remains low. The AAFP members fear that even a permissive universal recommendation would cause trouble in reimbursements and increased office visits. Immunization is already a loss leader incurred by physicians as a courtesy to their patients, and there is already some disagreement among physicians about its value.
- The Workgroup hoped to have a time frame to avoid an open-ended statement and to ask the involved parties what activities would be feasible over that time period.
- Despite evidence to support a universal recommendation, logistical problems include the presence of thimerosal in vaccines, vaccine shortages, administration issues, and that ~18% of the physicians surveyed opposed the change. Use of the sequential IPV model was suggested instead, in which OPV use moved to IPV.
- Support for Option #2 included: 1) While the data on health burden are convincing, those on safety/efficacy are less sound. That information could be collected and support a recommendation; 2) It would be a disservice to the nation and the program if a vaccine shortage in the first year causes the recommendation to fail. A 1-2 year forewarning provides a better chance of success.
- Clarify the intent of the recommendation and detail what will need to be done to prepare, (e.g., data collection, recognition of challenges to be solved first, etc.), to relieve some of the caretakers' anxiety about what will happen.
- Estimate the vaccination rate under Option #2, and determine if there is a target below which universal vaccination would not be worthwhile, to help manufacturers calculate the supply and demand issues of that option.

There was general agreement that Option #2 was preferred by the Committee. However, more clarity is needed about the further information needed before ACIP can make a recommendation, and three years is too long to wait to recommend. The June ACIP meeting will include an update on the education plans integral to Option #2 and on the status of VFC coverage for that option. There was interest expressed in hearing the Canadians' experience regarding feasibility, vaccine supply, uptake, etc., when they dropped their influenza vaccination recommendation from age 65 to 6 months of age. However, Dr. Marchessault reported that there were not yet enough data in hand to relate that.

2002 Recommendation for Control and Prevention of Influenza. Dr. Carolyn Bridges reviewed the time line for ACIP recommendations to ensure their *MMWR* publication by April 25. And in 2003, the first draft will be presented in October to allow a second meeting in February to revise anything required. Aside from the pediatric influenza discussions, the primary changes to the recommendation discussed by the Workgroup included: 1) the availability of vaccine doses with reduced thimerosal content; 2) the timing of vaccination; 3) the wording on the vaccination of pregnant women (define "expert"); 4) an update on vaccine strains and vaccine coverage levels; 5) additional details on influenza diagnostics, and 6) updated references.

Thimerosal (page 11 B, section on influenza vaccine composition) issues discussed include:

thimerosal use; primary concern is over use of thimerosal-containing vaccines in infants aged <6 months and among pregnant women. PowderJect-Evans will soon produce some reduced-thimerosal content vaccine, but it is not FDA-approved for use in children aged <4 years, and no influenza vaccine is FDA-approved for use by pregnant women. Due to limited availability of the reduced thimerosal vaccine and its recommended age groups, the recommendation only advises about the reduced-thimerosal vaccine availability without stating it as a preference. The Workgroup found no demonstrated harm and recommended no change in influenza vaccine recommendations based on IOM or the ACIP/AAP/AAFP joint statement. *The ACIP members had no objection to this approach.*

Vaccine coverage (page 13-14): was 66% overall in 1999 among those aged ≥65 years. Challenges remain to vaccinate high-risk children, health care workers and high-risk adults aged <65. Regarding vaccination of children, the Workgroup suggested: adding detail in the section on effectiveness and safety of influenza vaccine information specific to young children; moving the section on vaccination of children forward in the document; suggested language for the timing of vaccination among all children aged 6-23 months; advise that influenza vaccine can be offered to children who will be 6-23 months anytime in the influenza season and are encouraged to be vaccinated. The influenza vaccine is not approved for use in children aged <6 months.

Discussion. It is unclear for what age group the vaccination would be recommended. *Recommendation: Clarify the document such that one cannot administer the vaccine to children aged <6 months; recommend one dose or two (the Edwards study's one dose was effective). Decision: recommend two doses if <9 years and vaccinated for the first time as currently stated in FDA-approved indications.*

For *vaccination of household contacts of young children* (page 16), the Workgroup offered three options:

1. Household contacts and out-of-home care givers to those aged 0-23 month olds:
   Disadvantage: Implementation (no way to ensure that contacts out-of-the-home will be vaccinated); feasibility of vaccinating 8 million in two birth cohorts plus adults, totaling 12 million vaccinees; undoable recommendations threaten ACIP credibility.
2. Household contacts and out-of-home care givers to those aged 0-<6 months;
   Advantage: Clearly indicates concern about children aged ≤6 months, who cannot be vaccinated. Satisfactory until a universal recommendation can be issued in 1-2 years for the 6-23 month age group.
   Disadvantage: Implementation again; this essentially translates to a universal recommendation; credibility could be damaged (particularly with vaccine supply issues); defer discussion until June.
3. No mention of contacts of young children.
   Disadvantage: Ignoring the problem will not resolve it, and questions from the field will continue.

Discussion included:

- "High" and "higher" risk need more definition.
- Avoid the inconsistency of encouraging vaccination of those aged 6-23 months old, but recommending it for their parents. Clarify that language.

Dr. Zimmerman moved to support Option #2, using wording to "encourage" vaccination of families of infants aged 0-6 months. Dr. Brooks seconded the motion. The committee agreed to review the issue in detail at the June or October meeting(s).

Conflicts: Wyeth, Aventis Pasteur, Evans
Vote
In favor: Zimmerman, Smith, Tompkins, Salamone, Brooks, Offit, Word.
Opposed: Deseda, Levin, Birkhead, Modlin.
Abstained: Rennels
The motion passed.

Timing of Vaccination. Dr. Bridges referenced the recent years' need to issue supplemental ACIP influenza vaccine recommendations due to vaccine delivery delays. Changes in timing were recommended to vaccinate those at highest risk people and health care workers first, followed by others later in the season. The Workgroup offered three options, all of which would also encourage vaccination in December and beyond as well:

1. Not change the vaccine recommendations, adhere to the optimal vaccination period of October through the end of November.
2. Use the tiered protocol, to vaccinate those aged ≥65, other high risk people aged ≤65, and health care workers in October, all others in November.
   Advantage: Consistency; most similar to what has been done in the past two years of delivery delays; appropriately prioritizes health care workers; avoids the confusion of potentially two community campaigns for risk and non-risk populations;
3. Retain the current recommendation to vaccinate from October through November, but defer campaigns directed to healthy adults (e.g., workplace vaccination programs) until November.
   Advantages: Consistency: avoids several risks of a phased system: 1) potential vaccine wastage when people do not return for later vaccination, potentially decreasing coverage; 2) supports vaccine delivery in community settings to better reach minority groups and high-risk populations impeded by health system barriers to vaccination (BRFSS data support that non-immunization relates more to lack of education on that necessity than to SES); allows the lead time necessary to plan and execute worksite or community campaigns.

Discussion included:
- Healthy children aged 6-23 months would be included in the early immunization.
- Aventis Pasteur's vaccine return rates have been relatively stable over time.
- Influenza itself is a unpredictable variable, but distribution is predictable; option #2 supports that consistency.
- Ms. Deborah Wexler suggested stating clearly that October/November are optimal vaccination times, but "to improve vaccine coverage and utilization, particularly among high risk persons and health care workers, influenza vaccine should be continued to be offered in December through March."
- Add a section on needed research.
- Note in a footnote that whole cell vaccine is not used for young children in the U.S.

Dr. Modlin checked for consensus and determined by a show of hands that Option #2 was preferred.

Conflicts: Wyeth, Aventis Pasteur, Evans
Vote:
In favor: Smith, Tompkins, Salamone, Deseda, Brooks, Offit, Levin, Birkhead, Word, Modlin.
Opposed: Zimmerman
Abstained: Rennels
The vote passed.

Dr. Zimmerman moved that the ACIP adopt the influenza statement with the suggested options and changes. Dr. Word seconded the motion.

Conflicts: Wyeth, Aventis Pasteur, Evans
Vote:

In favor: Smith, Zimmerman, Tompkins, Salamone, Deseda, Brooks, Offit, Levin, Birkhead, Word, Modlin.
Opposed: None
Abstained: Rennels
The motion passed.

Adult Immunization Schedule
Dr. Vishnu Sneller reviewed the February 19, 2002 draft of the Adult Immunization Schedule. It was developed by a subgroup of the Adult Immunization Workgroup , the Harmonized Adult Immunization Schedule Group, which included representation of the ACP, IDSA, AAFP and ACOG. The schedule is a brochure, similar in format to the childhood schedule. It is age-based for persons aged >18 years and for persons with special conditions or chronic diseases. Its footnotes present additional information for the disease on the condition-based schedule and additional notes on the brochure's back cover for the age-based schedule.

The current draft has been accepted by the ACOG and was in review by the AAFP. Last presented to the ACIP in October 2000, alterations had been made according to the comments received:
- The cover indicates that the schedule is a summary of the recommendations of the ACIP and shows the DHHS affiliation
- The titles were changed to be consistent and include the word "adult," without indicating the age range.
- The chronic disease and conditions schedule adds a footnote (J), stating that it is prudent to withhold MMR from persons with extreme immunosuppression (<200 CD4 T-lymphocytes or a CD4 plus percent of total lymphocytes <14, or diagnosed with tuberculosis, invasive cervical cancer or recurrent pneumonia), and adds the MMWR reference.
- The Workgroup suggested that the schedule be annually reviewed at the October ACIP meting and published in the MMWR by December or January.
- Next steps: prepare a report to be published in the MMWR, present the document draft to ACIP in October, 2002 for comment and revision.

Professional Society responses included:
- AAFP: Generally positive, still reviewing it line by line. However, the AAFP has not supported meningococcal recommendations in the past,
- ACOG: endorsed enthusiastically as a step toward an age- rather than risk-based schedule.
- ACP: need for time to review. They requested more data to support the Lyme and meningococcal recommendations, and questioned the reality of recommending this in view of significant vaccine supply or delay issues (e.g,. influenza and tetanus).

The Workgroup was congratulated on their work. *Comments* included:
- Review the color scheme again (e.g., the green color on the childhood schedule is associated with catch-up, but represents influenza vaccine on the adult schedule).
- Add the citations to the footnotes to allow the reader to look them up; perhaps include the ACIP web site address.
- Since a CD4 <200 is only one indication, just say "AIDS-defining condition."
- Allow for flexible footnotes to present all the partners' perspectives (e.g. on meningococcal and tetanus) and to allow all to endorse the schedule.
- Add to footnote 8 the advice developed for MMR and varicella, to not vaccinate pregnant women or those planning to become pregnant in the next four weeks, and if pregnant and susceptible, to vaccinate as early in the postpartum period as possible.

Dr. Birkhead **moved to adopt the schedule with the suggested changes**, and the motion was seconded by Dr. Smith.

No conflicts.
Vote:
In favor: Smith, Zimmerman, Tompkins, Salamone, Rennels, Deseda, Brooks, Offit, Levin, Birkhead, Word, Modlin.
Opposed: None

Abstained: None

Harmonized Childhood Immunization Schedule
Dr. Margaret Cortese, of the NIP, presented the recommended childhood immunization schedule. Its time line was approved by the AAFP and AAP in a conference call. The 2003 schedule should be ready for the professional societies' approval by the June meeting. Any concerns of the ACIP, AAP, or AAFP will be addressed in October, and any schedule modifications will be presented for final ACIP approval in October and November, and the schedule will be submitted for publication in mid-November and published in January 2003. Dr. Evans reminded CDC of the need, space allowing, to reference the availability of the NVICP and that VAERS should be contacted with any adverse effect reports.

Update on Vaccinia (Smallpox) Vaccine Preparedness
After a short break, Dr. Hal Margolis reported on the smallpox response plan and guidelines. These are working documents to be updated periodically. The plan identifies federal, state, and local public health activities necessary to respond effectively to a confirmed case of smallpox. The CDC director, in consultation with the DHHS Secretary, may implement all or portions of the plan. The plan provides for surveillance and lab activities to identify or rule out smallpox; notification procedures for suspected cases; a smallpox control strategy (vaccine deployment, case and contact information, to finish it patient care and isolation, and quarantine). Specific guidelines for surveillance, contact tracing and outbreak investigations, vaccination, isolation and quarantine, decontamination, laboratory diagnosis, specimen collection and transport; and communication for health-care providers and the public. The annexes address the clinical presentation of smallpox, patient care, vaccination clinic procedures, adverse event reporting, and suggest pre-event planning activities for state/local public health authorities. The framework with which to receive, review, and implement revisions to this document is in development. One vehicle will be contact with immunization-related committees such as ACIP, as well as consultations by CDC with professional organizations and content experts.

An algorithm is provided, developed with the AAP, IDSA and others, that guides the differential diagnosis of smallpox as a vesicular-pustular rash illness. It is quite specific and details the availability of laboratory diagnostics for varicella, the most common smallpox look-alike. Color coding helps to indicate the points in diagnosis at which the health department or CDC's involvement is called for. It does not identify the early smallpox phase of the infectious macular-papular rash illness. Those diagnostics do not exist, and if they did, they would have to be modified to address an intentional release of smallpox in 'weaponized' formulation.

The question of sites for vaccinia diagnostics is in discussion, involving the Association of Public Health Lab Directors. Just one problem is the lack of well-qualified, real-time PCR tests that can speciate the orthopox viruses. Follow-up questions then are where besides CDC they should reside and how to maintain quality control and proficiency testing.

The plan's vaccination and control strategy utilizes the "ring vaccination" or "search and containment" protocol that successfully eradicated smallpox. Cases are found and a ring of immunity is built around them by vaccinating their contacts and those persons' contacts as well. The cutoff point is a public health and operational judgment, as done in any outbreak. This approach also minimizes adverse events, an important point since the vaccine effects are acceptable only in the face of disease, and it provides the most efficient use of vaccine supplies.

Success depends on the vaccine supply, personnel resources and readiness, and effective use of other outbreak control measures, which include isolation and quarantine, and personal protective equipment for the caretakers.

The smallpox vaccination guidelines provide for pre-attack smallpox vaccination only for laboratory or medical personnel working with non-highly attenuated orthopox viruses. These were identified by ACIP in 2001 as having a higher risk for exposure because of contact with smallpox patients or infectious materials, should an intentional release occur.

The current vaccine, Dryvax,® was released as an IND to allow the use of the 15 million-dose undiluted supply. Dilution studies are being done and a 1:5 effective dilution would produce 75 million doses. A vaccine,

ACAM1000,® in development by Acambis is a cell-culture-derived vaccine. Dryvax® is a calf lymph-produced vaccine. They are the same virus and adverse event profiles are expected to match. ACAM1000® will begin in use as an IND and a comparative trial for non-inferiority will be conducted. An initial production of 54 million doses is planned. Then, in ACAM2000, Acambis and Baxter will produced 155 million doses. Licensure is presumed after the Phase I, II, III trials, but efficacy cannot be demonstrated without disease circulating.

In June 2001, ACIP stated that "Because the risk of smallpox occurring as a result of deliberate release is considered low, and the population at risk for such an exposure cannot be determined, the risks of vaccine complications outweigh the benefits for pre-attack vaccination." An extrapolation of the population's susceptibility and the implications to routine vaccination was presented. Among older Americans, the concern is about higher prevalence of immunodeficient persons than in the past; and among children, it is the presence of eczema, which allows vaccinia to spread. Considering these, the adverse event profiles from the 1970s indicating a death rate of one per million vaccinated individuals would probably be higher today. Therefore, pre-attack vaccination was recommended by the ACIP for only laboratory or medical personnel working with non-highly attenuated orthopox viruses, who constitute a group of only a few hundred people.

In closing, Dr. Margolis posed three questions to the ACIP members:

1. Does our current increased preparedness preparation equate with increased potential for an attack?
2. Should selected groups with an identified higher risk of exposure to smallpox patients or infectious materials be vaccinated?
3. If so, how should these groups be defined and identified in terms of guidelines, which are not in the June 2001 statement?

Discussion included:

- *Were there any outcomes among the ~300 CDC employees who received vaccinia?* The year, multi-disciplinary smallpox response teams of ~20 people each were formed and the teams were vaccinated, but that has been stopped. The rationale was that, if a case of smallpox occurred, it would be identified by a CDC team. That prompted question #3.
- *The WHO guidelines define home confinement as "quarantine," which the bioterrorism health officer in California said would be impossible. To what degree is CDC working with local health departments, legislatures, etc., to address containment?* This was a major issue in many states. National disasters/emergencies initiate emergency control, but those issues are not yet resolved, although they are beginning to be examined. Most states have quarantine laws, and some model legislation was published recently. Even more difficult how to deal with cases may be hoaxes.
- *What is "weaponized" smallpox?* That is defined as "not natural disease."
- *What do we know about isolation in mobile population settings (e.g., jet travel)?*. in India, where much of the poorly immunized populations travel by rail, the last case seen in a major marketplace did not spread. There are several variables associated with spread. Anyone incubating can travel, but a person clearly with fever and heavy rash will not.
- CDC needs to reaffirm that if there are cases, CDC will quickly provide vaccine for PEP, due to high reactogenicity. This is covered in the large document Dr. Margolis referred to, but there is fear that patients will not be transported, labs will refuse to handle specimens, etc. A very simple and clear statement is needed that the vaccine will be made available to ensure that some people will be willing to take the chance.
- *The strategy needs expansion to address who will take care of children if adults are sick.*
- *What was the uptake in rats, and were there adverse reactions in the CDC staff?* The take was 100%. There were some very aggressive primaries reactions that appeared to be cellulites, but were just aggressive primary takes. The inexperience in recognizing that is part of CDC's renewed learning curve.
- Healthcare workers should be a primary group for immunization, since in Europe's post-smallpox epidemic era, >50% of the remaining smallpox introductions were in that group. There is also some question about Russian work on anthrax, but it is suspected that the stories related had been distorted by pairing anthrax and smallpox in the descriptions.
- Pre-identified locations and staff for bioterrorism response is essential to ensure that at least a small group can be in place to begin with. In general, the larger states are forming such teams, while the smaller states

are still looking to CDC. The general sense of the states that there should be some limited pre-event vaccination was also reported.

- In the coming year or perhaps even longer, ACIP will have to address how to engage communities and the public in such planning. Among the challenges are having vaccine immune globulin available (VIg) to handle complications and defining the rationale used in selecting the groups to be vaccinated in such a way that is acceptable to those hearing it (e.g., public, politicians). Those decisions need to be made consistently across the country and explained well.
- Dr. Heilman reported good data from the NIH dilution studies for 1:5 and 1:10 dilutions. Over 10,000 safety data points were entered, relative to the ~600 persons vaccinated. All the take rates were good, but there is no evidence ready for release on whether the local reactions were less severe. The data are being double-checked, and the second set is hoped to be ready by August. An article will be published as soon as the data are inserted, and all the data are shared with CDC.
- Decisions on who to vaccinate must be made, especially as supplies increase. ACIP should reconsider its prior statement to decide if the text should be changed.
- *The vaccines contracted for are in tissue culture; how will FDA approach the Phase 1,2,3, studies?* The vaccines are being grown in diploid cell lines, as done with varicella vaccines, using the same process of cell banks and viral seeds. Phases 1-3 will begin with safety evaluation, then expand to include immunogenicity, and Phase 3 will address safety data. Without circulating smallpox, there is no clinical endpoint study, but the old immunogenicity and take rates would be used for evaluate Dryvax for efficacy. The numbers needed to test for unusual events will be indicated in the first two phases. Typically, a live viral vaccine trials involves thousands of participants to produce a safety database. But even several thousands cannot address rare events such as post-vaccination encephalitis.

Dr. Modlin suggested continued work with the Smallpox-Bioterrorism Workgroup led by Dr. Helms. Recognizing the changes in NVAC and ACIP membership, a small group will be formed to re-examine this Workgroup to reconstitute it to work along the agenda outlined by Dr. Margolis.

Vaccine Supply Update
Mr. Dean Mason, Chief, NIP's Program Support Branch, Immunization Services Division, provided an update on vaccine supply.

Td: Wyeth-Lederle's cessation of Td production left Aventis Pasteur (AP) as the only major national producer, with some supply from the University of Massachusetts Medical School, being distributed through FFF Enterprises. Td is only being shipped to emergency departments (ED) and not to individual practitioners. Td demand continues to exceed supply and tetanus is the limiting factor in the production of DTaP, Td, T, DDT, DTaP/Hib. But even with a ~11-month production time, the need during national emergencies can still be met, as demonstrated on 9/11. A return to the routine schedule could occur by late fall 2002.

DTaP: The estimated national need of DTaP is 18-20 million doses; ~18.5 million doses ertr supplied in CY2001. A disproportionate shortage occurred in the public sector, even though it constitutes 60 % of the market, and among private providers who depend on public purchased vaccine. This was principally a result of a decision by AP to prioritize supply to the private sector. About 750 million doses of DTaP vaccine on backorder were administratively canceled in January because the major supplier of DTaP vaccine, Glaxo SmithKline, had maximized their supply limit through CDC's contract. CDC hopes to have a new contract, now in negotiation, with AP and GSK by March 1. DTaP production by one company has been less efficient since the thimerosal preservative was removed.

Reports on the states' central depot inventories from September 2001 to January 2002 indicated 65% with zero inventory or less than a two-week supply. Only about 78% of the public sector's DTaP need is being met, mostly by GSK. AP is limiting its supply to private providers to up to 80 doses per physician per week, but that can be adjusted based on the practice's situation. NIP will continue to monitor the orders and to work with GSK and AP to prioritize the supply to the grantees most in need. A return to the full schedule for all providers may not occur in 2002, despite a previous estimate of a return to normalcy by fall. This situation could improve with the U.S. licensure of a widely-used a Canadian DTaP vaccine.

Pneumococcal conjugate vaccine supply: Future supplies are hard to predict, although the production issues allegedly caused by the vaccine's more-rapid-than-expected uptake has been corrected. An average 701,750 doses per month were shipped from January to August 2001. About 52% of the market purchase is through CDC's contract. There was significant month-to-month variance in both public and private sector supply in late 2001 and early in 2002. Backorders were reduced to about 135,000 doses in January, but inadequate supply raised backorders to 584,000 doses by February 15, 2002. From September 2001 to January 2002, at least one-half of the states' central depot inventories reported a zero or <15 day supply of PCV 7. The only exception was in the month of December. Shortages in both the public and private sectors and supply fluctuation will continue in the early months of 2002. Wyeth Lederle expects its 2002 production to meet demand, but inventory buildup may not be sufficient to return to the routine schedule before mid-year.

Varicella vaccine. The annual need for varicella vaccine is 6 to 7 million doses, or 500,000-583,000 doses per month. CDC's contract captures ~60% of the market. The varicella vaccine supply dropped from 6.3 million doses in CY2000 to 6 million doses in CY2001. The average monthly supply from January to October 2001 of 600,000 doses dropped 65%, to 210,000 doses between November 2001 and January 2002. The supply remains at record lows. Shortages are expected in all states in both sectors. To date, all orders received by December 21, 2001, have been shipped; leaving 325,000 doses backordered >15 days. An average of 60 days might be necessary to fill the orders for the next several months. Although the spring supply should exceed the monthly need, states may need to waive school, daycare or Head Start admission or attendance vaccination requirements with "immunization in progress" waivers.

MMR vaccine supply is the hardest to evaluate. The national need is 1.08 million doses and the CDC contract purchases ~60% of the market. The December 2001 supply of 1.2 millions doses, and the January-February 2002 averaged supply of ~734,000 doses was supplemented by a withdrawal of 700,000 vaccine doses from the CDC stockpile, and was not from increased production. Some states are receiving partial shipments. Delays in filling MMR vaccine orders will be ~15-40 days and will continue into March, when Merck predicts a significant supply increase.

Other vaccines: The meningococcal and hepatitis A vaccine supplies should be sufficient to meet all requests. Of the other Merck vaccines, Hib orders are currently being filled, but soon may take up to 60 days to fill, at least through May. Hepatitis B/Hib orders will take 30 days to fill at least through April, and hepatitis B vaccine orders will have a 6-week backorder, at least into April.

Mr. Mason outlined the NIP's response to the vaccine shortages. This included working closely with ACIP on vaccination schedule adjustments; working with projects and manufacturers to prioritize orders to those most in need; collecting project inventories monthly and prioritizing shipments to those reporting a less than 15-day inventory; limiting vaccine supply to 30-45 day amounts; and providing regular updates on the situation.
The projects are responsible for accurately reporting their central depot inventories; ordering only in 30-45 day increments; adhering to ACIP schedule recommendations, even in the absence of an immediate shortage; considering their budget amounts when ordering vaccines; not making "side deals" with vaccine manufacturers; and planning for supply disruptions that are likely to continue for at least the next three to six months.

Impact of the Vaccine Shortage: Preliminary Findings
Ms. Shannon Stokley, MPH, of the NIP, reported on two recent studies of the impact of the shortages on state immunization programs and providers.

Immunization Program Manager Survey. In January, the NIP surveyed immunization program managers on their shortages of PCV7, DTaP and Td. 54 programs (96%) responded. Most of the programs reported changes in their vaccine distribution (85% for DTaP, 87% PCV7, 96% Td) most of which involved limiting the amount ordered or distributing partial orders. A full 30% of the programs did not distribute information on the DTaP shortage to their providers, versus 6% and 4% for PCV 7 and TD respectively. The effect on school requirements was minimal for DTaP and PCV 7, ranging from 4-11%, the 48 % of school entry requirements were affected by the Td shortage.

Of other vaccines, 76% had shortages of varicella, 39% were short on MMR, and 11% were short on both Hib and

Hep B, respectively, or had no shortages at all. Many are suspending the varicella vaccine requirement for the next school year

In summary, most of the programs implemented changes in vaccine distribution for Td, DTaP, and PCV7; ACIP or state-specific recommendations for vaccine administration during a time of and vaccine shortage were distributed to providers; and almost have indicated changing school entry requirements for Td. The most prevalent supply problems were with varicella and MMR.

Immunization provider interviews were conducted January 21-February 1, 2002, at VFC and AFIX site visits. Thirty immunization programs participated (25 state, 5 urban) and 447 site visits were done. The interviews assessed the difficulties in purchasing vaccines, changes in distribution due to shortages, and the length of time no DTaP and PCV 7 vaccine was in stock. Most of the providers (69%) were in private practice and almost half (48%) had up to five providers.

Data collected on nine vaccines indicate that providers in general have more difficulty getting public purchased vaccine. *DTaP:* Since September, 68% had made none of the changes recommended due to the DTaP shortages; 6% ran out and suspended vaccination before they knew there was shortage; the fourth doses and fifth doses were suspended by 16 % in 11 %, respectively; and 4% implemented different policies for publicly- versus privately-purchased vaccine. *PCV 7*, 45% had adequate supplies; 17% ran out of vaccine before realizing there was shortage; the fourth and third doses were suspended by 28% and 17%, respectively; 23% vaccinated only high-risk children; and 5% implemented different policies for publicly- versus privately-purchased vaccine.
In summary, providers experienced greater problems receiving public purchased PCV7, varicella, Td, and DTaP compared to private purchased vaccines; ~25% of providers had to suspend administration of one or more doses of DTaP and PCV7 due to vaccine shortages; and providers experienced greater length of time with no PCV7 vaccine in stock compared to DTaP.

Discussion included:

- Dr. Peter requested that the data be provided to the committee, even if preliminary.
- The MMR supply problem is ameliorated, but not solved. After considering the varicella issues, the ACIP should consider recommendations in response to potentially short MMR supplies.
- *Did the 45% of programs that had not changed after the ACIP recommendation to withhold dose 4 know of that new policy?* That was not asked on the site visits. It may be that some vaccinated few enough children that their stocks remained sufficient. More analyses will be done by provider types, practice size, etc.
- The states with adequate supply have to decide if they should adjust their schedule anyway, further confusing the complex immunization schedule. Questions asked include whether dropping the DTaP dose 4 or 5 helps the supply, and about the differences in the recommendations (e.g., suspend PCV7 versus the last DTaP doses). Children may also be hard to recall to catch up their immunizations.
- **Dr. Modlin confirmed the committee's sense that no preference should be expressed for thimerosal-free Hep b and Hib vaccines, excluding DTaP due to continuing supply problems.**

Strengthening the Supply of Routinely Recommended Vaccines in the U.S.

Dr. Myers reported on the NVPO and NVAC meetings held the previous week on strengthening the vaccine supply. The supply issues addressed were: the delays in influenza vaccine production; shortages of Td, DT, TT, DTaP, pneumococcal conjugate, MMR, varicella, and anthrax; a limited supply of smallpox vaccine and no oral polio virus (OPV) vaccine for outbreak control; the transition to reduced-thimerosal containing vaccines; and changes in immunization recommendations risk cause reduced coverage and increased risk of disease.

The meeting's objectives were to assemble all the stakeholders to describe the scope of the problems, identify contributing causes and potential response strategies, and to develop a limited

number of pragmatic options for NVAC and the IAVG to consider further.

The strategies considered included 1) increasing (or perhaps restructuring) the financial incentives; 2) streamlining the regulatory process; 3) establishing government-directed programs (e.g., a national vaccine authority as advised by the IOM, or contracting for production); 4)using vaccine stockpiles; and 5) increasing liability protections, and other related issues such as intellectual property rights, licensing agreements, and non-U.S. markets

The common themes heard at the meeting included that vaccines are under-valued. A restructuring of financial incentives is needed. Setting national vaccine priorities and creating stockpiles to smooth out supply disruptions seem like obvious opportunities. Although there are barriers, communication across stakeholder groups is needed to recognize evolving problems in order to develop effective responses.

The initial assessments of the specific strategies were: 1) reassessing the manufacturing incentives may be important, but requires careful consideration to prevent unintended consequences; 2) while issues were identified, there was support for the current regulatory processes; 3) a more unified federal participation is desirable, but government-owned or -directed solutions are less likely to accomplish long-term goals; 4) developing vaccine stockpiles are a high priority to help address temporary disruptions of the supply that will undoubtedly occur again; and 5) the National Vaccine Injury Compensation Program (NVICP) has been important and effective in stabilizing the market.

Next steps identified included: 1) the Assistant Secretary has asked the IAVG to develop both short and long-term strategies to strengthen the vaccine supply; 2) NVAC is to publish the workshop proceedings and provide input on the development of options for consideration; 3) the GAO is also considering vaccine supply issues.

Discussion included:

- Discussion of the successes or failings that resulted from the blueprint for the vaccine program for the 1990s would be helpful.
- Stockpiles are important to prevent crises in public health. It has become clear that even vaccines with multiple manufacturers should be stockpiled, to buffer a manufacturer's departure from the market. However, the influenza vaccine presents an ongoing challenge since its composition changes yearly.
- The workshop concluded that there are no simple answers to the supply questions such that, for example, a technical problem could easily be fixed by a technical resolution.
- To ameliorate providers' sense of confusion about the escalating antigen shortages and possible alterations to the routine schedule, clear communication is needed.
- Mr. Reilly assured the committee that the manufacturers take these issue seriously and are addressing them. But he reminded them of the complexity and regulation of the vaccine manufacture process, a combination that has increased the challenges in the last few years. He suggested using the term “strategic inventories” rather than “stockpile.” Manufacturers normally hold inventories sufficient to compensate for the variability of

the manufacturing process, which can change from month-to-month, to ensure a steady supply to the marketplace. But now that there are no inventories they are shipping as fast as they produce. He supported a CDC inventory stockpile to serve as a national supply buffer.

- The workshop discussed how to keep manufacturers in the market. The involved issues include that the price is kept low for older vaccines, but the manufacturing expenses may increase to maintain CGMP. This may lead to a business decision that is not helpful to public health. There was an effort to identify the basic problems to develop a strategic approach at the workshop. One valuable outcome was note of the common urgency to ameliorate the problem, even as viewed from different perspectives.
- *Was consideration given to using products manufactured abroad in the event of the shortages, or any incentive to their market entry?* It was agreed that quality products that parents will trust are needed. The regulatory bar rises to ensure that good manufacturing procedures are current. Dr. Midthun expressed FDA's encouragement of license applications to enable FDA to study the data. The question is what incentive might encourage that process.
- Barriers to communicating the status of the vaccine supply were discussed at the workshop. All agreed that more proactive monitoring would be helpful. Earlier notification of supply interruptions was a key recommendation.
- One of the ten proposals to strengthen the vaccine supply, outlined in the industry perspective paper developed by Wayne Pisano of Aventis Pasteur, was an industry pledge to advise CDC well in advance of any changes in vaccine supply due to either production problems or marketing decisions. Another interesting paper was also noted, released by Boyd Clark of Aviron, on the development of intranasal influenza vaccine. His point was that the costs of developing vaccine by a large manufacturer are lost in the overall overhead. However, he calculated the actual cost to bring vaccine to licensure at $700 million. This may be higher than most vaccines, but it relates to the question of incentives for manufacturers who need a high vaccine price to achieve a return on investment.

Varicella Vaccine

Dr. Jane Seward outlined the burden of varicella disease. In the pre-vaccine era, ~4 million cases of varicella a year resulted in ~10,500 hospitalizations and 100 deaths a year, most among healthy children and adults. The highest incidence occurred in the preschool and early elementary age groups; there was increased risk of exposure and incidence among children attending child care; and the highest risk of severe disease occurred in adolescents, adults, and immunocompromised persons.

Most cases of varicella occur among children, accounting for two-thirds of the hospitalizations and about half of the deaths. The highest risk factor for developing severe disease and hospitalization occurs among adults aged ≥20 years, followed by adolescents. Adults also have the highest risk of death, followed by children aged <1 year and those who are immunocompromised.

Age-specific varicella incidence, according to NHIS data from 1990-94, is highest among those aged 1-4 years. A well-defined doubling of risk in childcare settings was published ten years ago, and other studies showed that the highest incidence of varicella occurred in preschool and early elementary school among the age groups 2-6 or 3-7.

The ACIP recommended one dose of varicella vaccine for all children aged 12-18 months and for susceptible children age 19 months to 12 years. Vaccination is also recommended for susceptible persons with close contact to persons at high risk for serious complications, for health care workers, for family contacts of immunocompromised persons, and susceptible persons at high risk for exposure or transmission. It is also desirable for other susceptible adolescents and adults. Post exposure vaccination within 3-5 days is recommended, as is vaccination for outbreak control. Vaccination with 2 doses, 3 months apart, should be considered for HIV-positive children with CD4 counts >25 , and school and child care requirements were advised.

In the last two years, 6 million doses of varicella vaccine have been distributed each year, well above the total of the birth cohort. As of February 2002, 27 states have implemented child care or school entry requirements for varicella vaccine. As of September 2002, four states will add school to their existing child care requirements and four more will implement child care or school requirements or both.

In response to the shortages, three states have suspended child care and school entry requirements, and many other states are considering that. Some states are conducting January or February "roundups" for school requirements rather than waiting for the summer. The process for dealing with shortages varies from state to state, but actions already implemented include preferential vaccination for children aged <2 years, those in child care, and vaccination of cohort(s) covered by school requirement (Arkansas) and in child care (Alaska).

Post vaccine epidemiology shows an 80% decline in disease in active surveillance sites, which has accompanied increased vaccine coverage. Similar patterns are seen in states doing passive surveillance. There has been a great decline of incidence among all age groups to 2001, but the active sites also show a shift in peak incidence from ages 2-6 to 5-10 years of age.

Dr. Seward summarized that there has been a 75%-85% decline in incidence reflected in both active and passive surveillance systems. Evidence of heard immunity is seen in disease declines among both unvaccinated and vaccinated children in 11 North Carolina daycare centers (Clements et al) and declines in cases among infants and adults in active surveillance sites. In areas with high coverage, the highest incidence is among children aged 5 to 10 years; in areas with moderate coverage, highest incidence may be at lower ages. Children aged ≤1 year have a lower incidence and low risk of severe disease, but adolescents, adults, and high-risk children (i.e., those with HIV, leukemia, asthmatics on steroids, etc.) are at the highest risk for severe disease.

Groups to consider for prioritization of varicella vaccine use are:

- Susceptible health care workers and family contacts of immunocompromised persons.
- Susceptible adolescents (13 years+), adults and children with high risk conditions.
- Children 19 months to 12 years (catch-up).
- Infants 12-18 months (routine).

Merck statement: Dr. Don Beeman, of Merck Vaccine, expected that individual physicians with shortages over the short term should be caught up by late spring. Merck pledged to work continuously with the ACIP and CDC to resolve the backorder issues, and hoped to catch up by late spring. They are shipping out as soon as possible, and are prioritizing with CDC.

Dr. Seward presented a draft recommendation developed with the AAP and the states:

"There is currently a shortage of varicella vaccine throughout the United States. Vaccine providers should therefore prioritize their use of available supplies. If administration of varicella vaccine is delayed, vaccine providers should implement a call-back system when vaccine is available. In the United States, while a vaccine shortage persists, recommendations for use of the limited supply of varicella vaccine are:

1. Maintain vaccination of healthcare workers, family contacts of immunocompromised persons, adolescents (13+), adults and high risk children (< 10% annual doses)
2. Maintain routine childhood vaccination but delay the dose until 18-24 months unless the child attends a child care center
3. Maintain vaccination of susceptible children 5-12 years with focus on children entering school and adolescents aged 11-12 years. States should provide guidance on priority cohorts for vaccination
4. Maintain vaccination of children 2-4 years who attend child care centers"

Discussion included:

- This is too complicated, although it essentially just says to continue all that is normally done except for changing the routine dose from 12-18 to 18-24 months.
- The recommendation may outlast the shortage.
- This is a stop-gap measure to help some providers not run the vaccine. If the recommendation is postponed, a lot of vaccine will be needed.
- Options discussed: 1) ACIP could delegate the NIP to issue the recommendation if necessary, as done for DTaP in the past, but NIP felt that some action was needed quickly; 2) select option #2, but qualify the recommendation with "*IF"* the provider has a vaccine shortage. However, partial recommendations are ineffective, and is hard to monitor the vaccine supply. 3) Issue a strong single recommendation to delay the dose except for children in child care.

Dr. Zimmerman supported option #2 without confusing the issue with the mention of child care. He **moved to recommend that varicella immunization be delayed until the child is 18-24 months old.**

Conflicts: Offit, Levin, Rennels
Vote:
In favor: Smith, Zimmerman, Tompkins, Salamone, Deseda, Brooks, Birkhead, Word, Modlin.
Opposed: None
Abstained: Offit, Levin, Rennels
The vote passed.

NIP will notify when this recommendation is no longer necessary and state clearly where that notice will be published. In fact, NIP was advised to place all information on all vaccine delays in one spot on their Website. This recommendation would apply to all providers, not just those currently experiencing shortages. It was hoped that many providers will follow suit, but realistically expected that there will be some partial adherence.

MMR Vaccine

Dr. Melinda Wharton suggested providing guidance to providers who have a shortage of MMR (not all providers), hoping that this shortage will be short-lived. Normal supplies are expected in spring . The proposed language was:

> "If providers are experiencing difficulty in obtaining all the MMR they need to fully implement the current recommendations for the MMR vaccination, ACIP recommends: 1) deferring the second dose of the MMR vaccine series, and 2) instituting tracking systems so that unvaccinated persons can be identified with supplies improve."

Discussion included:

- A concern expressed over suspending measles immunization requirements, it was clarified that this was not the intent.
- Aside from the spring kindergarten "roundups," schools will probably let children begin school conditionally, with a physician's note that the immunization is in progress.
- Many providers do the second MMR vaccination at 4 years of age; delaying that to age five may allow the school entry dose to be given. However, there was concern that this would be confusing, particularly since most states have a kindergarten entry immunization requirement.
- The projections of a return to normal supply in the next 3-4 months included the use of the stockpile as well as production.
- Dr. Myers noted that this was a profound change in immunization policy, and that measles, mumps and rubella are important bases of the national immunization program. He advised better understanding of the use of the stockpile in the situation, in light of future likely stockpile decisions.
- Added concern is the continued controversy about the potential adverse effects from MMR vaccine. The least disruptive recommendation may be to defer the immunization to ages four and five.
- The simplest message would be to delay the second dose, which should be clearly communicated. As done with DTaP, ACIP could empower NIP to do so if needed.

The decision was deferred to the morning. The meeting adjourned at 6:45 p.m., and reconvened at 8:00 the following morning.

FEBRUARY 21, 2002

Old Business

Dr. Orenstein requested that NIP be authorized by ACIP, as done for DTaP, to issue a

recommendation on MMR usage if the supply shortage becomes apparent. The program was not seeking a change in the schedule, but guidance from ACIP, due to concern over the spot shortages. **Dr. Smith moved to accept the language as proposed**, and the motion was seconded. Dr. Abramson stated that the AAP would place that on their Website. The text of the advisory was as follows:

> "If providers are experiencing difficulty in obtaining all the MMR they need to fully implement current recommendations for the MMR vaccination, ACIP recommends: 1) they defer the second dose of the MMR vaccine series, and 2) institute tracking systems so that unvaccinated persons can be identified when supplies improve, and recalled for vaccination when supplies improve."

Conflicts: Merck

Vote:

In favor: Smith, Zimmerman, Tompkins, Salamone, Deseda, Brooks, Birkhead, Word, Modlin

Opposed: None

Abstained: Offit, Rennels

Rabies Vaccine

Dr. Brooks reported the goal of the Rabies Workgroup to develop a supplemental statement to the current ACIP recommendation on Human Rabies Prevention. This began in response to the recent discontinuation of Imovax® Rabies ID vaccine, as reported by Dr. Charles Rupprecht at the last ACIP meeting. Imovax® is the only rabies vaccine licensed for intradermal pre-exposure use.

Pre-exposure vaccination (PEV) is considered for those at high risk for exposure, such as veterinarians, animal control officers and laboratory staff.

The proposed supplement statement, which was designed to not encourage off-label use, was as follows:

> "This statement is a supplement to the Advisory Committee on Immunization Practices recommendations regarding human rabies prevention in the United States(MMWR 1999; 48:rr-1). As of March 2001, Aventis Pasteur discontinued sales of Imovax Rabies I.D. vaccine, manufactured for intradermal pre-exposure use. Administration of rabies vaccine is intended for individuals who are high risk for rabies exposure(e.g. rabies research, production and laboratory staff, veterinarians, animal control workers and wild life workers, travelers to endemic dog rabies areas, etc.).
>
> "**While this intradermal preparation is no longer available, three other products are licensed and available in the United States for either pre-exposure or post-exposure prophylaxis, administered as a 1.0 ml intramuscular dose: human diploid cell vaccine; purified chick embryo cell vaccine; and rabies vaccine absorbed. Further research is encouraged on the development of additional safe, effective and economical biologicals in human rabies prevention.**

There was no discussion.

VOTE:
In favor: Smith, Zimmerman, Tompkins, Salamone, Rennels, Deseda, Brooks, Offit, Birkhead, Word, Modlin.
Opposed: None
Abstained: None

The vote passed.

Household Contacts of Individuals: Influenza Vaccine
Dr. Word related to the committee the language developed by Dr. Bridges and the workgroup to provide more consistency in the advice on household contacts of children aged 0-<6 months. They suggested that, after the 5 bullets and added text discussed on the previous day, the following be added:

> "In addition, because children aged 0-<23 months are at an increased risk of influenza-related hospitalization, vaccination **is encouraged** for their household contacts and out-of-home caretakers, particularly for contacts of children aged 0-<6 months, since children aged <6 months cannot be vaccinated against influenza (see "healthy young children")."

Conflicts: Wyeth, Aventis Pasteur, Evans: Rennels
Vote:
In favor: Smith, Tompkins, Zimmerman, Salamone, Deseda, Brooks, Birkhead, Word
Opposed: Offit
Abstained: Rennels
The motion passed.

Dr. Tom Zink, of GSK, discussed the manufacturers productivity, especially regarding DtaP. In 2000, 7 million doses were produced for the U.S., and 12.2 million doses in 2001. There is an ability to ramp up the production to the national need, but there are other ways to improve vaccine supply. Efficiency in manufacturing methods include pre-filled syringes, which increase the amounts of vaccine available at bedside by 10% as opposed to the loss of one dose from 10-dose vials, due to the draw loss.

Agency/Committee Updates

National Immunization Program (NIP). Dr. Orenstein related good news on the containment of vaccine preventable diseases (VPD) but for one complication: congenital rubella. Decreases in VPD incidence occurred across the board, reflecting an annual morbidity in 2001 that ranged from 96 %-100% less than that of the 20th century. The most dramatic reduction was a rubella, with 47,000 cases reported in the 1960s versus 19 cases in 2001. This paralleled the efforts by PAHO and Mexico to incorporate rubella into their immunization programs. Coverage is at or near record-high levels, with only dose 4 of DTP remaining at 83%. This was not affected by supply problems: those children were born between February 1998 and November 1999. The disease risk to the population is addressed by the combined series (4:3:1:3:3), which now

includes varicella. There was some decrease in the use of the combined series of the last two quarters of 2000 versus those of 2001 (78% to 75%), especially for that last, most complex combination.

Section 317 appropriations for 2002 are $627.9 million ($75.3 million over 2001), for vaccine purchase, operations/infrastructure, prevention activities, and global immunization activities. The proposed FY2004 funding is level. Infrastructure funding rose from $139 million to states in 2000 to $182 million in 2001, and to $200 million in 2002-3. The goal is $220 million to achieve the IOM recommendations.

NIP engaged the IOM conduct a study to: 1) determine the role of public and private agencies and providers for vaccine purchase administration, price determination for new vaccines and finance strategies, and 2) the current levels of need for vaccines by children without health plan coverage; finance issues regarding the time lag from recommendation to implementation (as seen with pneumococcal conjugate vaccine), and 3) to look at the current levels of need by children not covered by any system, perhaps drawing on the experiences of other fields which finance medical devices and supplies to find a solution applicable to the vaccine field. The Committee Chair is Dr. Frank Sloan, the study director is Dr. Rosemary Chalk. The first committee meeting will be March 11-12 in Washington D.C.

Discussion included:

- *Why were there 10-fold decreases in reported rubella cases this year?* The speculation is that in the last few years community wide outbreaks in foreign-born adults were transmitted to U.S. communities, providing indigenous transmission of imported virus. The rubella activity outside the U.S. has also decreased , perhaps due to a waning rubella cycle and increased immunization outside the U.S. Surveillance improvements effected due to bioterrorism surveillance will probably produce some increases. Dr. Ciro De Quadros' and PAHO's work in reducing the circulating rubella in South America was commended
- The IOM study will address the clearly significant racial and SES disparities in immunization, and adult immunization.

Department of Defense (DOD) Dr. Diniega outlined DOD's anthrax vaccine immunization program. With FDA approval granted on January 31, DOD is considering resumption of the anthrax vaccination program. Currently, the limited vaccine supply is being used only for personnel at special exposure risk and for PEP. DOD had reported safety studies two years ago, and he provided to more information today on 18 more safety studies. He offered to report in more depth if the ACIP so desired. Dr. Snyder added note that DHHS has been working with DOD on anthrax vaccinia absorbed (AVA) issues. DOD will make some amount of that information available to the civilian sector.

Food and Drug Administration (FDA) Dr. Midthun reported on two VRBPAC meetings. In November, they considered efficacy endpoints to support licensure of a human papilloma virus (HPV) preventive vaccine. Cervical intraepithelial neoplasia (CIN) 2 or 3 was selected as a

primary endpoint. Accelerated approval was supported, but confirmatory studies should then show an impact on CIN 2-3 in conjunction with virology, the more definitive endpoint. In the January meeting, they considered the selection of influenza strains for the next year and retained the H3N1 and H3N2 strains present in last year's vaccine; the B strain selection was deferred to the March 6 meeting. VRBPAC also approved a supplement to the BioPort anthrax vaccine supplement, as well as approved their renovated facilities and the supplement to their package insert. An HBV vaccine is on the horizon.

Dr. Snider added that the selection of the H1N1 strain was more complicated due to a new strain emerging in Asia that is moving toward the Victoria strain and is not well covered by the current vaccine strain. A quadravalent vaccine was discussed but considered not feasible, although one is used in Europe, because the U.S. uses 15 micrograms per strain. If another valent is incorporated, another 15 would have to be added, since the immunogenicity of cutting other strain components is unknown.

National Institutes of Health (NIH) Dr. Carole Heilman reported NIH's plan to study the use of Dryvax® in dilution studies and its use in the pediatric and geriatric communities. They are also considering potential problems with Dryvax® use among other immunosuppressed populations (e.g., modified vaccinia anchors – MVAs). Similar studies will be done to expand data being developed by Acambis and CDC, relative to children and the elderly. She continued that anthrax studies are being conducted with DOD, particularly with USAMRIID and others to produce and test a viable vaccine for safety. The protocol is being developed and NIH hopes by the next meeting to have the recombinant protective antigen (RPA) vaccine trial under way. The development and purchase of RPA is in NIH's 2003 budget, and an RFP has been issued to manufacturers. NIH's approach will be adjusted based on comments received from them.

Workgroups have been held about NIH's studies among immunocompromised populations. The current leaning is to use alternate vaccines such as MVAs rather than Dryvax® among them. MVAs have been used as vectors in a number of HIV studies, so their safety is established. Immunization of immunocompromised patients it would be post-exposure or post-event, not pre-exposure. Dr. Myers recalled Dr. Margolis' mention of vaccinia immunoglobulin, and which CDC considers will be needed for those potentially undiagnosed after an event. On February 4-5, a blue ribbon panel met to discuss the NIH research agenda. High priority areas discussed included plague vaccine. NIH will meet with DOD and other collaborators to explore a joint program on that. Dr. Diniega added that the only area of potential difference between the agencies would be on vaccine priorities, but they have already accelerated smallpox vaccine development.

National Vaccine Program Office (NVPO). Dr. Myers reported that NVPO and the National Vaccine Advisory Committee (NVAC) had recognized Dr. David Satcher's contributions as CDC Director and Surgeon General/Assistant Secretary of Health. Dr. Myers will provide part-time continuity to NVPO in the short term, and Drs. Art Lawrence and Dixie Snider will assume the NVPO's oversight until the new director is appointed, hopefully the next month or so. He applauded the interagency cooperation that has been ongoing to address the vaccine supply

shortages, and particularly thanked the vaccine manufacturers for their considerable effort.

The NVPO funds $6 million per year to conduct research on unmet immunization needs. This year one-third went vaccine safety research. Pandemic influenza preparedness continues to be a major funding area, as well as adult immunization and disparities. The NVAC defined immunization for adolescents and pregnant women as a new research area this year, supported by the Interagency Vaccine Workgroup (IAVG).

Workshops help included that on vaccine supply described on the previous day. Upcoming workshops will discuss new vaccines and pandemic preparedness. He hoped that the latter's technical documents will be finalized and cleared soon; the state and local pandemic preparedness plans are posted on the NVPO Website.

A presentation on global polio elimination under way was presented by Dr. Walter Dowdle. The laboratory inventory of potentially contaminated specimens is underway. Dr. Helen Slater, the new Assistant Secretary of Health, will hold a meeting in March to develop support to complete the inventory by the end of the year. The next stage will be to increase the level of biocontainment for work on polio specimens.

NVAC. Dr. George Peter reported six new NVAC members and the committee's review of an update on thimerosal in vaccines. A workgroup to discuss the formation of policy under uncertainty will be formed when the NVPO director is appointed. Major related issues to be addressed revolve around bioterrorism, anthrax, smallpox preparedness, and the need to involve not only physicians but also the public, to reduce anxiety and improve compliance. The NVAC Smallpox Workgroup also will be revived to discuss those issues.

A workshop on the vaccine supply will be held February 11-12 and NVAC recommendations will be crafted to address the pending supply crisis. Progress was reported in the development of immunization registries. Many programs/projects are developing programs and strategies, but currently only ~20-25% of children are in a registry. The goal is 95 %. The overriding need is funding, which is hard to get in the current climate. The Standards for Childhood/Adolescent Immunization Practices were revised, will be circulated for comment, and will be published in the *MMWR*. They were originally issued in 1993 and complement the Adult Immunization Practices, which are in publication now.

Completed topics by the IOM Immunization Safety Review Committee include the role of multiple immune antigens. The next topic suggested was hep b vaccine and neurological disorders. Recent rulings by CMS on compensation for vaccine administration in Medicare have caused concern, reducing that compensation from $10 to $4. NVAC needs to examine what is the appropriate level of compensation for health-care providers to deliver vaccine. The new reimbursement reflects the undervaluation of immunization and is inconsistent with the standards' encouragement of immunization. Finally, Dr. Peter thanked Dr. Myers for his service of the last four years.

Discussion included note that those instrumental in getting the new bioterrorism money can help in pandemic preparedness. For example, California is calling this "catastrophic preparedness." The ACIP requested a summary of the presentation to be given to NVAC by Mr. Scully of CMS to discuss compensation. The presentation was suggested by ASH Dr. Slater, who supports immunization.

National Vaccine Injury Compensation Program (NVICP). Dr. Geoffrey Evans welcomed Mr. Salamone to NVAC's membership, and anticipated his more active participation as a consumer representative in Washington D.C. meetings as well. He then presented the NVICP's monthly statistics as of January 31: 1) an average of ~24 claims/month; and 2) "new" vaccines claims for hep b, 389; Hib, 4; varicella, 18; rotavirus, 189; pneumococcal, 1; and DTaP, 48. Ten pre-1988 claims remain and the trust fund balance is $1.76 billion.

He outlined the process for obtaining compensation. To prove a Vaccine Injury Table (VIT) "table injury," legal presumption of causation applies if the the condition occurred in a specified time period unless another cause is present. Proof of causation is the same standard as is used in tort regulation ("absent negligence"). Proof of significant aggravation is required.

A Notice of Proposed Rulemaking was issued on July 13, 2001 to modify the VIT and the "Qualification and Aids to its Interpretation" (Aids). No written comment or oral testimony was received on it. The final rule is under review by DHHS to add a vaccine or condition to the VIT. That would involve eight years or retroactive coverage and a two-year window in which to file claims.

Proposed changes: add intussusception under a new rotavirus category; remove *h. influenzae* type b (Hib) polysaccharide unconjugated vaccine from the table; remove early onset Hib disease and residual seizure disorder from the Aids; an add pneumococcal conjugate vaccines to the Table with no specified condition.

NVICP-related legislation:

- Vaccinate America's Children Now Act (HR921): bipartisan support.; reduces the tax for each "dose" of vaccine for DTaP (to $.75 from $2.25) and IPV ($.75 to $.25).
- HR 1287, Vaccine Injured Children Compensation Act, proposes using the burden of proof standard of the Veterans claims processes (damage noticeable by a "fair and impartial person"). It incorporates several legislative proposals endorsed by the Advisory Committee on Childhood Vaccines (ACCV): 1) extension of the statute of limitations to 3-6 years from the date petitioner "first knew or reasonably should have known....may have been eligible for compensation;" 2) payment of interim fees and costs (to attorneys); 3) compensation for family counseling; and 4) compensation for establishment/maintenance of trusts.
- The NVICP Improvement Act of 2002, raises the death benefit to $300,000 from $250,000, acknowledging inflation, and provides for more generous compensation for lost earnings.

NVICP Oversight. A bipartisan report issued by the House Government Reform Subcommittee

in October 2000 included three recommendations: 1) review the VIT to ensure it reflects current science; 2) continue developing and implementing speedy and fair informal dispute resolution options and practices; and 3) determine a reasonable alternative standard for non-Table cases.

The last is a challenge for the NVICP, as the original table had 7 antigens and 8 listed conditions. Only two of the five vaccines added in the 1990s list conditions on the VIT. Almost all claims are filed alleging non-table conditions. The difficult burden of proof makes compensation unlikely, which indicates the need for standard relaxation to **adjudicate causation-in-fact claims.**

At the last ACCV meeting in December, an alternate standard was proposed based on the Agent Orange Act. This uses a "positive association" standard, which is less rigorous way of determining a "relationship." And IOM review of the scientific basis is under way. The relationship standard would applied to non table-claims only and has a lower threshold for awards. It requires a "reasonable" biological mechanism to indicate plausibility and a positive association. In those regards, IOM review is the key contributor.

The AAP also proposed not changing the VIT, since the finding of a relationship is not deemed evidence of a causal link. This change would not affect VAERS' reportable events table or the VISs, unless the finding of a strong relationship would be put in the VIS. The AAP thought this proposal to be less adversarial, likely to resolve more claims in the petitioner's favor, and provide consistency in the adjudications.

The IOM has established an NVICP Committee for ongoing reviews. Its ten-year contract provides for periodic reports every two years on the alleged relationships (which will be selected by the Secretary in consultation with ACCV). Any person or entity may petition the Secretary. Periodic reviews of the Table will be done every 4 years, regarding assessments of biological mechanism, positive association, and time frame, and the development of methodologies for determinations.

Thimerosal litigation. Claims have been filed in state court alleging thimerosal-related injury from childhood vaccines. This avoids filing a claim with the NVICP, which requires $1000 in damages; but since no neurological damage has been demonstrated from thimerosal content and vaccines, no damages can be proven. However these cases are claiming that thimerosal is a vaccine "adulterant," which excludes claims under NVIC Act. DHHS and the Department of Justice are **preparing a "statement" to be filed in state cases disagreeing with this interpretation**, disputing that thimerosal is an integral part of the product.

Two types of suits have been filed: a traditional tort claim alleging specific child's injury and seeking lifetime medical care, and 2) a medical monitoring" class action suit with a few plaintiffs representing a large group of unnamed individuals. One class includes 30 million individuals. Since there is no **currently known neurologic injury, they are asking for periodic checkups to detect that in the future. C**laims have also recently been filed alleging thimerosal-related neurologic damage: of 38 claims in FY 02 alleging autism, six were thimerosal-related

Discussion included:

- Committee members expressed general disbelief that "positive association" would be sufficient. One member's analogy was to his son's conviction that his "lucky shirt" makes his favorite team win.
- *How does the IOM information filter down?* Under the Agent Orange Act, the Secretary of Veterans Affairs categorizes and decides who receives benefits. Some categories are automatically compensable, subject to legal requirements, so they do not constitute a "table" injury, but are eligible for compensation. The IOM input is a vehicle with which to put some science into this decision-making. More discussion is needed before this becomes law, but the IOM will provide the court with guidelines to support the decision-making process. This will enhance the scientific credibility in the long run, help the process be less adversarial, and perhaps satisfy parent groups somewhat.
- Dr. Chen wished that new technology and more reasonable approaches would be used rather than going back to the Agent Orange methods. He noted that the excise tax is not used to prevent the injuries from occurring, which was part of the intent of the law as well as compensation. While the AAP proposal is helpful and CDC will work with them, a major fundamental gap remains unaddressed. The process of adding injuries to the VIT is only possible through post marketing studies, which require funding to explore such topics as thimerosal, MMR and autism, and to evaluate them before claims are made. One to two percent of the trust fund should be allocated to such research to prevent future injuries, particularly since technologies such as genomics can now assist those studies.
- Dr. Halsey expressed concern that a relationship or association can be so easily established, particularly since some physicians and scientists are willing to state relationship based on dubious science. While he agreed that there is room for relaxation of the process, the resolution needs to be scrutinized closely before being effected.
- More refinement will be necessary regarding how the evidence is characterized in discussing the strength of the evidence along a spectrum of criteria, some or all of which can be met. Some people may only be able to show a temporal association, but also an outcome severe enough that society wishes to compensate the family and child. While that is understandable, in the credibility of the immunization program, science, etc., could be threatened if that decision is accepted as proof of a causal association. Clear articulation is essential about whether the compensation decisions are based on a causal association, or are made because society wishes to help despite an absence of data or only limited data to support a temporal association. It will be important to avoid inappropriate assumptions that certain events are proven to be associated with vaccines when in fact they have not.
- There was agreement to the previous statement. The original intent of the program, supported by studies, changed with the evolution of the claims such that presently only 5% are supported by evidence. However if litigation goes back to the tort system, one of the program's primary goals for been defeated.
- There is great confidence in the IOM, but some of these committees' membership criteria will block participation by many who are knowledgeable in the field (e.g., if a nominee was ever a member of the ACIP). There was agreement that it would be preferable to

just provide children with disabilities with optimal care, which would make these issues moot.

National Center for Infectious Diseases (NCID) Dr. Alison Mawle noted an article in the January 2002 *American Journal of Virology* on the virology of avian influenza transmission to humans. Sixteen H1N1 viruses were isolated in 1997; two in the 1999 outbreak; and two human H3N2 viruses circulating in 1997 were sequenced. Data were examined to explore any links between the six nonstructural genes, and very similar internal viruses were found in the H5N1 and the H9N2 avian viruses found in quails.

The internal genes of human and avian viruses were compared to gene banks of other avian viruses, revealing that all those going into humans and those circulating in Hong Kong belonged to one clade[1] – and in fact, were identical, even though they appeared over two years and had different lineages. And, while it had been presumed that internal sequences distinguished between human and avian amino acids, four amino acids were found in humans that were thought to be only avian, as well as mixed sequences those of formerly considered avian or human.

The internal genes of avian viruses that went into humans were closely related to each other and differed from other human influenza A viruses. The similarity between the sequences suggests little selective pressure. They are not transferred between humans, but from birds to humans, clearly shown by avian amino acid residues in human isolates. Re-evaluation now is needed to clarify exactly what is meant by host-specific amino acid residues. Pathogenicity studies indicate that the H5N1 viruses were a more specific disease because the internal genes of this particular cluster allows them to grow well in host cells. The amino acid sequences of these internal genes are being studied to explore their functions.

The ability of avian virus to grow in human cells poses implications for a pandemic scenario. However, it may be possible to predict which avian subgroups may pose the most implications to a pandemic. For example, the current Hong Kong H5N1 virus' internal genes are not of the type to transfer between species. Influenza genetic mixing/matching is also being done in animal studies (mice/ferrets) to explore which genes confer transmissibility. Later, in discussion, Dr. Mawle clarified that the internal genes are internal proteins, all of which are common in sequence for human and avian viruses.

National Center for HIV, STD, and TB Prevention (NCHSTP): Dr. Timothy Mastro updated the committee on the on HIV trials underway in North America and Thailand among injecting drug users. Dr. Walter Dowdle chaired the efficacy/safety advisory board which reviewed the preliminary study results. There was no evidence of higher efficacy, but the trial did not reach the lower level either. CDC held a consultation in January on the use of a partially effective HIV

[1] Clade: A relationship of sequences (not necessarily just of viruses) from a prototype, for which the length of time from divergence can be estimated.

vaccine in the U.S., which is hoped to be published in *Clinical Infectious Diseases* in the next few months.

Rotavirus Vaccine and Intussusception

Dr. Myron Levin reported on the Rotavirus Workgroup's consideration of recommendations for the use of rhesus rotavirus vaccine (RRV), RotaShield.®

Background. The FDA approved the RRV in August of 1998. Its use was recommended by ACIP in October of 1998, and by the AAP that December. ACIP followed with a recommendation for universal use in March of 1999, and both organizations warned of a possible outcome of intussusception (IS). A unique VAERS code was created for intussusception and listed as a potential rare event with RRV. CDC recommended temporary suspension of RRV use in July 1999 and the AAP withdrew its recommendations the same month. In October 1999 Wyeth Lederle withdrew RRV from the market. The same month, IS analyses based on VAERS data were presented, involving a cohort and case-control study. ACIP withdrew its recommendation with the caveat that the risk-based analysis supporting that action in the U.S. may not be applicable in the developing world.. Estimates of vaccine use were of ~1 million doses administered, ~540,000 age-eligible infants vaccinated, and vaccine coverage at <13%.

Since then, worldwide research has been conducted on the epidemiology and natural history of of intussusception and rotavirus infection, the diagnosis/management of IS, animal model studies of virus-induced IS, and laboratory/clinical **studies of candidate oral vaccines. Workshops were held** by NIH/NVPO in January 2000 and by NVAC/NVPO in September 2001. The latter was summarized by Dr. Peter as the October 2001 at ACIP meeting. The case control and case series studies indicated strong, temporal, and significant associations between RV and IS. The attributable risk was approximately one case per 10,000 vaccinated, primarily after dose one. The September 2001 workshop also included ecological studies, which detected no epidemic of IS after RRV was introduced. However, the low rate of vaccine coverage provided limited power to detect an outcome. The workshop discussed whether RRV may have a “triggering" function, a hypothesis suggested by the study principals to explain the discrepancy between ecological and other studies.

A Rotavirus Workgroup was formed of ACIP members, staff of CDC, FDA, HRSA, and representatives of the AAP, AAFP, NMA, IDSA, and NVAC/NVPO. Two conference calls were held, as well as two meetings in June 2001 and February 2002, and about half the workgroup members participated in the September workshop.

Materials considered by the Workgroup since the October ACIP meeting include articles (Simonsen, L, et al, ecological analyses; Sansom, et al, parental acceptance of IS risk; Murphy et al, no evidence of “triggering”; Barlow et al, seizures after MMR and pertussis vaccines); review of letters over this controversy to the Workgroup and in the *New England Journal of Medicine* and *Lancet;* the draft Workshop report; an extended follow-up study of the original cohort by Dr. Philip Rhodes; and a pediatrician survey by Dr. Larry Pickering. Manufacturers' perspectives were provided by Merck and GSK, and other commentaries and primers were also consulted. A February teleconference reviewed all the information including the ecological studies and all

materials were sent to the ACIP.

The conclusions reached were:

- A selective recommendation was rejected again due to: inadequate information on high-risk groups; treating minorities will be difficult both politically and with unlikely compliance by minority caretakers; and the safety profile for a selective recommendation was unclear and would also be insufficient for manufacturers' purposes.
- Discussion of a universal recommendation reached agreement to the benefit of having an oral vaccine useful in the U.S. and elsewhere. A risk-benefit analysis is needed, but has not been done (e.g., to estimate the education costs to "sell"oral rotavirus vaccine to the people who will use it, or for use in ED visits due to fear of vaccine side effects).
- There was general agreement to the attributable risk of 1:10,000 and that further use of oral RRV will require education to the public and the field.
- The value of RRV in developing countries is undisputed; the effect of U.S. policy on this is unclear.
- The Workgroup favored no change to the current ACIP policy to withhold a recommendation for the use of RotaShield® among U.S. children. There was a minority opinion that a permissive recommendation could be possible, but was not the best solution due to: 1) no vaccine available to use; 2) unlikely to be heavily used in the current environment; and 3) the difficult and risk to its credibility for the ACIP to recommend on a vaccine nonexistent at the present time.

Manufacturer Perspective. Mr. Reilly, speaking for Wyeth Lederle, agreed to the presentation and added a few points.

1. Wyeth will follow ACIP's direction, but Wyeth's reservations about a permissive recommendation are even stronger. A permissive recommendation will not clear its use in the public; only a universal use recommendation will do that; and even with that, given the publicity, usage would be low.
2. Litigation is an issue the manufacturer has to consider if providing a vaccine with a known trigger or side effect.
3. Wyeth is prepared to reinstitute manufacture with a new universal recommendation, but that would be a big task. They probably would have to go back through FDA's process again and the former production facilities were reassigned to other product production.
4. A universal recommendation is needed to signal the vaccine's use in developing countries, where no one knows the effects of IS and there is a lack of medical care.

AAFP and AAP perspective: There is no movement to change the current recommendation.

Discussion included:

- Some developed countries are now thought to have some studies on a rotavirus vaccine, including a risk-based analysis.
- Dr. Tom Vernon, of Merck, expressed his conviction that a rotavirus vaccine will be put before ACIP again, by GSK and/or Merck. He was very pleased with their current trial, which produced one case of IS four months after dose 4. He and Dr. Zimmerman expressed their appreciation of Dr. Levin's chairmanship of the Rotavirus Workgroup.
- Dr. Barbara Houk, of GSK, reported limited trials underway, which they plan to expand in developing countries in the near future.
- Dr. Albert Kopikian, of NIH, stated that developing countries will not use a vaccine that is not used in the developed countries. Wyeth is not interested in manufacturing without a universal recommendation. NIH will make it available to developing countries, but they will not use it if it is banned in the U.S. However,

he believed that a permissive recommendation would have a good effect in the developing world, freeing up production of this vaccine in the third world where it is most needed, where 1000 children die of rotavirus daily. The 1999 statement mentioned that it should not bear on the vaccine's use in the developing world, but that had no impact on the WHO. He urged the committee to approve a permissive recommendation.

- Dr. Chen presented some evidence provided at the September NVPO meeting. A hypothesis was developed by researchers studying OPV and intussusception. They found, in contrast to the U.S.' lack of seasonality for intussusception, that Cuba's was seasonal, peaking in April and then declining. Hygiene in Cuba also is better than in most of the third world, which suggests that the epidemiology of Cuban intussusception differs. In fact, this difference could extend to developing versus developed countries, in light of the fact that the rate of GI infections in the very clean U.S. environment is very different than that what might exist in a tropical setting. The risk for intussusception after rotavirus vaccine may also differ.
- Dr. David Moranz, of NIH, asked if there were any situations under a permissive recommendation in which Wyeth might reconsider making the vaccine, even though the use may be low. Mr. Reilly was unsure of exactly what was being asked, but responded that, given circumstances of history and publicity, a permissive recommendation in the U.S. would prompt very low usage by parents and practitioners and not validate its use.
- Dr. Roger Glass, of NCID, was heartened that Merck and GSK are moving ahead to test the vaccine in both developed and developing countries. In the discussion of rotavirus vaccine, all have agreed to its importance, and indications are clear that this discussion will return. Dr. Levin's and the Workgroup's efforts to air the issues fully have been very important and positive.
- The incidence of 1:2500 to 1:10,000 sheds new light on the problem and supports a permissive recommendation. Many pediatricians still see the risk of IS as a positive way to raise awareness of it in the first 2-3 weeks after vaccination. Wyeth's discounting of the needs of third world countries was seen as insensitive in one comment.
- It is hard to do anything since ACIP began with a universal recommendation and then withdrew it. In future, a permissive recommendation that would allow population data collection could be preferable to an immediate universal recommendation. On the other hand, offering a permissive recommendation as means to get more safety data is problematic. Physicians look to the ACIP for a clear message as to whether a vaccine should be used, and permissive recommendations do not engender a lot of use.
- Dr. David Fedson, of Aventis Pasteur, thought that if a market could be developed in third world countries, Wyeth might be attracted back to the market (e.g., by GAVI). He also noted that the ACIP is not the world's arbiter, and that many vaccines used in the world at great odds with ACIP recommendations.
- *Would FDA license this vaccine now?* Dr. Midthun stated that post-licensure research always produces new data, which may indicate serious but rare events that could never be detected pre-licensure. So FDA constantly evaluates the new information and updates the package inserts. The November 2000 Vaccine Safety Workshop also discussed using a permissive rather than universal recommendation, since it is always desirable to know more before licensure than is normally possible. Perhaps there should be a transition period between vaccine release and a universal recommendation. She noted, finally, that the very serious event of VAPP was warned of on the OPV label, but the vaccine was still used until the decision to transition to IPV was made.
- Dr. Snider noted pragmatically that the ACIP recommends to the ASH and the CDC director, who then have accept or reject the advice. They would have to be convinced that a permissive recommendation is wise.
- Dr. Dick Ward, of Children's Hospital, Cincinnati, OH, suggested consideration of what will happen with the next two vaccines under development. Since the risk has now been set at 1:10,000, it will be very difficult for the companies developing RRV to establish that their vaccine will not cause any intussusception. He suggested for the future that ACIP not set the bar so high that, no matter the number of children involved, there will never be a chance of another universal recommendation.

Dr. Modlin **moved that the ACIP make no change to its 1999 policy on the use of Rotashield,®** and the motion was seconded.

Conflicts: Offit, Rennels, Levin
Vote:

In favor: Smith, Zimmerman, Tompkins, Salamone, Brooks, Birkhead, Word, Modlin
Opposed: Deseda
Abstained: Offit, Rennels, Levin

The motion passed.

Dr. Levin continued his presentation, noting the future research needed related to rotavirus vaccine:

- Better information on rotavirus morbidity, hospitalization and mortality (stratified)
- Better information on IS, stratified by age, risk factors, region.
- Animal models in which to study IS and provide correlates of protection for new candidate vaccines.
- Better methods for early diagnosis of IS and its treatment.
- Determination of the clinical or virological correlates of vaccine complications.
- An alternate approach to live oral RRV vaccine (e.g., parenteral).
- Determination of the benefits/limitations of oral rehydration therapy and breast feeding (treatment/prevention).
- Completion of (sufficiently) large clinical trials of candidate vaccines.
- Reliable information on acceptance of oral rotavirus vaccines by care givers and professionals.
- Can a public health forum be created to weigh the risk/benefits (e.g., cost effectiveness) of candidate rotavirus vaccines against other strategies, to know what is acceptable, by enabling manufacturers and others to work outside the agencies' various "silos" (e.g., determine by type of recommendation and target group)?

Dr. Modlin asked if that would be helpful to the FDA. Dr. Midthun said that public consideration of all these issues would benefit all, but she would have to check with FDA leadership. One of the things they consider is risk-benefit, and this is a broader, societal basis risk-benefit being considered.

Discussion included:

- The NVAC workgroup on making decisions in the presence of uncertainty will address risk-benefit as a central issue.
- The question is the level of risk that is acceptable. More broadly, rare risk of rare disease is not as well accepted as common risk. The Rotavirus/Intussusception Workshop's point was that IS is a major problem in the world pediatric community, more than febrile seizures. The ACIP could recommend holding such a forum.
- It is important for the public and practicing physicians to know that this problem is being addressed, so that when the education piece is implemented, they will know that it has been well thought out.
- In fact, this involves another broad issue, cited in the need to engage the public in dialogue about the smallpox vaccine. Those issues extend beyond childhood vaccines. Other disciplines outside the vaccine community have published textbooks on how to engage the public on controversial issues. They should be consulted.
- Empirical research is also needed on how people view and make risk decisions.
- A transient phase and methodological tool with which to detect risk would be of use. For example, the pre-licensure trials indicated the possibility of an IS risk, prompting the creation of that code. Without that kind of fortunate happenstance, perhaps data mining tools could detect such a potential problem. CDC and FDA are exploring that, and have found that as early as December 1998, before the first 1999 report to VAERS, a signal could have been detected. This methodology could be presented to the ACIP.

Dr. Levin continued his report:
Manufacturers' concerns:

- Potential low profit for domestic rotavirus vaccine, but high development costs and slow uptake (even with a universal recommendation) due to safety concerns; rotavirus is not perceived as a serious medical problem; and there is a preference for oral rehydration.
- Uncertainty in requirements for a vaccine; what risk of vaccine-attributable IS would be offset by prevention of rotavirus disease and death?
- Desired action by public health authorities: more accurate evaluation of rotavirus disease burden, better

definition of IS risk factors and improved diagnosis and treatment; universal recommendation for rotavirus vaccines that have an acceptable risk, and an education program (government and professional societies) to foster acceptance of any licensed rotavirus vaccine.
- Include vaccination in the VFC and VIC programs.
- Additional obstacles to new vaccines: providing a permissive recommendation before a universal one (i.e., a trial period); and licensing second vaccines through a shorter regulatory path.

Discussion included:
- Mr. Reilly commented that, as they do not have a second vaccine, his company would not be one of the responding companies. But, regarding the investment issues, the manufacturers are comfortable with the R&D risks this business entails. That is not more of a burden than normally seen. But RRV presents a difficult situation because the side effect quantified for RotaShield® has affected other products as well. If this becomes a new parameter, what size must future clinical trials be? There is also the conundrum that, while the ACIP recommends only for the U.S., it is also a global reference body. As pressures increase to produce vaccines faster than historically, the role of advisory committee preference becomes a big issue.
- Dr. Peter commended the Rotavirus Workgroup's conclusions and its workshop and recommended that their deliberations be written up as an ACIP or independent statement for dissemination to the public.

Dr. Levin also thanked the Workgroup and Dr. Trudy Murphy for her research contributions. He suggested that the Workgroup not be disbanded, but just stop working, in anticipation of future related issues.

Update on Thimerosal Issues
Dr. Roger Bernier updated the committee on the progress to provide a thimerosal-free vaccine supply in the U.S. When the IOM committee took a different approach than that of the ACIP, an ad hoc ACIP workgroup was formed in October 2000 drafted a recommendation to cease use of these vaccines by March 31, 2002. However, the changes in the DTaP supply delayed issuance of that statement, and the supply is still not normal. Since the Hep B and Hib supply is adequate, the ACIP may wish to pursue a different course for those.

Mr. Dean Mason presented a chart of the thimerosal-containing vaccines/toxoids in the pediatric schedule and under the CDC contract (not all of which are licensed in the U.S.). NIP estimated the amount of thimerosal in provider vaccine inventories in a survey conducted September 20, 2001 to February 20, 2002. The targets were a convenience sample of providers getting site visits from public health officials across the country. Inventory counts were done of all refrigerators for DTAP, Hib, and hep B pediatric vaccines. The thimerosal classification was based on the lot number information, which was verified by the manufacturers.

In September 2001, 225 sites were canvassed, and 447 by February 2002. The decline in thimerosal-containing vaccine went from 5.6% to 1.9%, from 33,500 doses out of 63,600; to 2,796 doses out of 149,147. These were delineated by DTaP, DTP, Hib, hep B-Hib, and hep B. Hep B rose from 4.95% to 7.5%; the proportion that is pediatric (10 microgram) versus adolescent versus adult (5 microgram) still requires evaluation. However, the NIP thinks that most of it is pediatric.

During the visits, the providers were surveyed about thimerosal-containing vaccines in their inventories. Of the 447 interviews, 83.5% reported no thimerosal-containing vaccines in stock at any time since October 2001. Only 25.3% said they were aware of the "voluntary exchange programs" implemented by GSK and Merck to replace the thimerosal-preservative vaccines with thimerosal-free ones. Only 2.9% had exchanged vaccines, with the following reasons given: unaware of the program, no thimerosal-containing vaccines in inventory; not worth the effort; will exchange after expiration.

The NIP's conclusions were that:
- The amount of thimerosal-preservative containing pediatric vaccines in provider inventories is small and continues to decrease.
- Thimerosal-containing pediatric vaccine inventories are almost totally comprised of hep B and DTaP/Hib (91%), and the latter is only licensed for dose 4.
- Less than 1% of all DTaP vaccines inventoried in provider offices contained thimerosal. One way to

accelerate that stock depletion could be to offer a systematic exchange program.

Dr. Bernier asked the sense of the committee as to whether anything further should be done. Dr. Modlin asked if, rather than not expressing a preference, the hep b vaccines should be delineated.

Discussion included:

- *There has been tremendous progress, and the main concern was over cumulative doses, not individual vaccines. Were any outliers in practices that might be administering thimerosal-containing vaccine?* Yes. Most of the hep b vaccine is in one location. It is not a widespread problem, although there may be other such clusters, but there does not appear to be a homogeneous distribution.
- Expiration will soon arrive for the DTaP and Hib vaccines, but the late DTaP shipments' life may extend into 2003. Dr. Vernon said that 99% of the last 5-microgram dose vials was shipped in May 2000, and the last syringes (1.2% of the total amount) were shipped in October 2001. He suspected that the remainder of the 5 mcg syringes were the centralized stock found, which is most likely to be used in school-based applications such as clinics, not among the newborn. But if ACIP suggested further retrieval, he would take that back to Merck.
- *Are more definitive studies on thimerosal planned?* Dr. Chen reported CDC's current process of coordinating a set of studies: 1) A follow-up of the VSD cohort children for a standardized battery of neurodevelopmental tests (2-3 hours) with the supervisors blinded to their thimerosal history. A pilot study is funded for FY2002 to work out the statistical and logistical issues of informed consent, test batteries to use, etc. 2) A planned case-control study of autism related to thimerosal exposure, in which children's school records will be evaluated by experts on diagnosing autism, and the same with VFC site charts linked to thimerosal exposure; 3) A range of other studies, some funded by NIH and FDA, and an automated screening of thimerosal exposure and outcomes.
- Dr. Plotkin lamented the "creeping scarlet letter" character of the thimerosal controversy. He noted that this discussion about a child receiving one dose of thimerosal was occurring despite the debatable scientific support of an association of autism and thimerosal, and there is no science at all that trace amounts of thimerosal is dangerous. Dr. Chen responded that CDC's studies would set a baseline with which to assess current exposures.
- Dr. David Salisbury of the U.K., reported their conduct of a case-control autism study that will record all outcomes as well, and two studies of thimerosal and vaccines. One of the latter is a WHO study using general practitioner research database (ongoing); and the other, by his department, is a study of the Bristol child cohort whose life events (and their mothers') are recorded. That is completed and he hoped to report on it soon.

Review of Antigen Overload

Dr. Paul Offit reported his and his collaborators' study data, (published in *Pediatrics*, 2002; 108:124-1290). He traced immunization from 1960, when children received two shots, to the year 2000, when children can get 20 shots by age 2 and as many as 5 shots at once. Parents are questioning the number of immunizations given. Interestingly, in parallel, the number of antigens in vaccines have actually declined, from ~3,215 in 1960 (e.g., IPV alone had 165) to 123-126 in 2000 (of which varicella has 68-70 structural proteins).

At question is whether too many vaccines overwhelm the infant's immune system. To answer this, the analysis centers on the number of antibodies involved. Within antibody molecules are variable regions that bind to proteins or polysaccharides, the diversity of which is determined by the genes. Those genes code for four hyper mutable regions, three of which are defined by DNA (variability, diversity, and joining). Many combinations of these genes allow for diversity ("combinodiversity"), along with the options of how the genes combine ("Junctional diversity"). Between those two variable, there can be 10^9 to 10^{11} different antibodies. Assuming ~10 antigens per vaccine and 10 epitopes per antigen, theoretically, one could respond to about 10^7 to 10^9 vaccines (million to billion).

But in terms of autoimmune overload in children, that calculation is limited in two ways: 1) The number of circulating B cells -- infants have <10, and could not possibly produce that number of antibodies; and 2) a child given a vaccine will have a detectable immune response in about a week, far too short a time for a single B cell to divide and produce enough antibodies to be detectable. The conclusion is that this calculation is an overestimation

of the number of vaccines to which a child can respond.

So, the question is, to how many vaccines can they respond? To answer that, Dr. Offit cited the work of Cohn & Langman (*Immunol. Rev.*1990; 115-90147) An antibody concentration of ~10 nanograms/mL is likely to be an effective concentration of antibody directed against a single epitope (which is an immunologically distinct region of a protein or polysaccharide that is recognized by an antibody molecule). Generating that 10 ng/mL requires about 1,000 B cells/mL of blood, which takes about 7 days. Assume in each vaccine 10 antigens and each antigen containing ~10 epitopes, each vaccine has ~100 epitopes, and each mL of blood has ~10^7 B cells. Then, dividing that 10^7 circulating B cells/mL by the 100 epitopes per vaccine, each person can respond to about 100,000 different vaccines at the same time. Therefore, the 11 or 12 vaccines given to infants in the first years of life will "use up" only ~.01% of the immune system.

And in fact, infants, children, adolescents and adults commonly encounter thousands of antigens all the time. An infant at birth encounters thousands of different bacteria to which they immediately begin to make an immune response. Studies demonstrate neonates' production of antibodies within days of birth in order to retain these organisms, which serve as a protective function (i.e., children with agammaglobulinemia are at much greater risk for invasive bacterial infection). And adults are colonized with ~ 10^{12} to 10^{13} bacteria -- a trillion to ten trillion bacteria, orders of magnitude more than the number of cells humans have in our body. We are constantly exposed to thousands of different antigens all the time.

Vaccines offer the advantage of linking infectious polysaccharides agents to a harmless protein to induce a protective response, a better immunizer than natural infection. Cytotoxic T-cells ameliorate disease; humoral immunity and antibodies are more important in protecting against reinfection, the function of vaccines.

However, this analysis does not consider that all epitopes are not the same (e.g., there are immunodominant epitopes); and that once a B cell changes from a naive cell to a memory cell, it cannot respond to new antigens. It also assumes a static immune system, which is clearly not true. David Ho demonstrated in 1995 that HIV-positive patients can produce ~2 x 10^9 naive CD4-positive T cells every day (for an adult, ~5 CD4-positive cells per mL of blood per second). Dr. Offit concluded that vaccines, for all practical purposes, could never "use up" the immune system.

He summarized that current studies do not support the hypothesis that multiple vaccines either overwhelm the immune system. Rather, young infants have an enormous capacity to respond to multiple vaccines as well as the many other challenges present in the environment. To parents who blame their children's health effects on a GI tract overwhelmed by antigens, he would describe the world as a deluge of bacteria and antigens, to which the infant is designed to respond.

Report of IOM Vaccine Safety Committee Review

Dr. Stratton provided copies of the IOM Vaccine Safety Committee's report, released the previous day at 4 p.m., on multiple immunizations and immune dysfunction. This was the third of the nine topics the committee is to review. The Interagency Vaccine Workgroup (IAVG) asked the committee to address the effect of multiple immunizations on an infant's immune system. In this study, the committee decided to refer to the evidence of biological mechanisms, rather than biological plausibility, in favor of more clarity and due to misunderstanding of what "plausible" means outside of vaccine safety concerns.

They defined multiple immunizations as related to the antigen load, not the number of injections. A single dose could have multiple strains of a single organism (polio vaccine) or antigens of multiple diseases (MMR); individual doses of several separate vaccines may be administered at a single health care visit or through repeat doses. All those definitions were used in the studies examined for epidemiologic evidence to represent the effect of multiple immunization.

Immune system dysfunction involves:

- Risk of infection (heterologous infection -- disease other than the vaccine addresses).
- Risk of allergic disease (asthma).

- Risk of autoimmune disease (type 1 diabetes).
- Two possible pathways to adverse outcomes: stimulation of harmful immune responses, or suppression of beneficial immune responses. The committee chose asthma and diabetes, both serious and involving frequent mention in parents' concerns.

The conclusions of the scientific assessment were as follows:

- Causality: The committee favored rejection of the hypotheses for both diabetes and allergic diseases. This was discussed at length and the committee tried to avoid a less-helpful finding of "no evidence for or against."
- Biological mechanisms:
  - *Autoimmunity:* The committee concluded that the theory of biological mechanisms capable of affecting an individual's autoimmunity was theoretical, but does not violate known biological principles.
  - The evidence on biological mechanisms will be experimental (in vitro, animal , models) or human clinical data (not epidemiological data) that, for example, wild-type infection causes the adverse effect or other vaccines cause adverse effects. To be most helpful, the Committee decided to summarize the evidence on biological mechanism as weak, moderate, or strong.
- Dr. Stratton shared the analytic framework of the process, which resulted in the following conclusions on the evidence: autoimmune disease resulting from molecular mimicry (theoretical only); bystander effect (weak evidence), loss of protection induced by homologous infection (theoretical), via the hygiene hypothesis (theoretical) and collective mechanistic possibilities (weak evidence).
  - *Allergic disease*: bystander effect (weak evidence).
  - *Heterologous infections*: Strong evidence for competition for antigen presentation. Data were also examined on carrier-induced epitope suppression.
- The IOM committee agreed that the infant immune system has the capacity to respond to antigens.
- In the significance assessment, the committee concluded that: concern about multiple immunizations has been and could continue to be of societal significance in terms of parental worries, potential health burdens of immune dysfunction diseases (or VPDs, if immunization is avoided), and future challenges for immunization policy-making.
- Public health recommendations
  - Policy analysis: 1) State and federal vaccine policy makers should consider a broader and more explicit strategy for developing recommendations for the use of (new) vaccines (e.g., continue the discussion begun in the Feudtner and Marcuse article of 2001); 2) a range of perspectives should be considered regarding the benefits, risks and ethical implications of vaccine use and immunization policies (i.e., include discussion of state mandates for vaccine use); 3) explore the merits of accommodating requests for alternate vaccine dosing schedules and the development of appropriate clinical guidance for any such alternatives.
- Policy reviews: None were recommended for the current childhood immunization schedule nor any license reviews based on concerns about immune system dysfunction.
- Research: Use existing knowledge; leverage it as possible; explore existing cohort studies and other knowledge regarding possible vaccine-related disease risks. Routinely collect immunization histories as part of study protocols and disease registries.
- Conduct basic science and clinical research on: 1) development of the human infant immune system; identifying genetic variability in human immune system development and responsiveness as pertains to genetic susceptibility to vaccine based adverse events; explore the feasibility of collecting data on surrogate markers for type I diabetes and clinical history of allergic disease in the vaccine testing and licensing process and in existing cohort studies of variations in the immunization schedule.
- Communication: DHHS should convene an appropriate panel to develop a research strategy to better understand why people believe what they believe about vaccines, in order to craft better risk-benefit communication strategies.

Finally, Dr. Stratton provided the committee's e-mail addresses for comment: www.iom.edu/imsafety; imsafety@nas.edu; her telephone number is 202-334-1342.

Discussion included:

- *Did the IOM consider yearly vaccination with three strains varied each year?* Not specifically, due to no data Generically, that would still count as multiple immunizations.
- *There is a disparity between heterologous infection in causality (6 studies with no effect and 1 questionable), but strong evidence of a biological mechanism from a string of multiple injections possibly affecting the risk of heterologous infection. What is that based on (e.g., number, quality of studies, different epitopes, etc), and how did the committee differentiate or equate those disparities?* Isolated biologic findings are not always reflected in a population study. The epidemiology did not seem to show an increased risk for these invasive conditions, an apparent contradiction, but sometimes a plausible biological mechanism does not happen due to other reasons.
- *Dr. Salisbury reported advising the IOM before they began work about the U.K. work on heterologous infection after MMR administration, but this was not in the report. He was also confused about the committee's charge, which was to look at multiple immunizations, since the report is specific to single immunizations and biological mechanisms for each vaccine in turn.* Some of the data were for multiple immunizations (e.g., MMR), although there may have been some also for single ones. The causality data were always on multiple immunizations.
- *Dr. Halsey cited the report's conclusion that there were biological mechanisms where multiple immunizations could theoretically predispose to autoimmunity, which is of concern to the public. What is not always understood is that there is always a host autoimmune response to an agent. He hoped the report would clearly explain this, since separating an autoimmune response from an autoimmune disease is critical.* That is covered in the background. That is why the evidence was found to be weak; there is no evidence that the disease follows the response. *Dr. Halsey encouraged the IOM to conduct small studies among physicians and providers on how they interpret the IOM's findings to ensure that they match.* The report's communications piece has been directed to writers and other professionals, but it is important to direct to the public as well, particularly as the IOM is an independent panel.
- *The interpretation for the general public must be clear that adverse events from multiple antigens is one aspect, but the other is that if immunization is abandoned and infections are allowed to occur, some may result in far greater adverse health consequences.* The IOM always discusses how VPDs could increase without immunization. The press coverage for this report discusses the real known benefits of the vaccines. *Beyond that, it needs to be conveyed that the effects of the diseases themselves are still unknown; for example, those effects could include autoimmune diseases.*

Update on MMR Issues

Dr. Orenstein introduced this report. The MMR immunization has been reviewed several times by the ACIP, AAP and IOM, and all concluded the present schedules' reliance on MMR should not be changed. Only MMR appears in the 2001 schedule, rather than any single antigen. There was preliminary review of some data from the U.K. and Ireland by the IOM and AAP in their reports, but a recent publication by all Uhlmann, et al detecting fragments of measles virus genomes in children with autism, compared to controls, created controversy in the U.K. Dr. Orenstein had written to Sir Liam Donaldson, the Chief Medical Officer of the London Department of Health, citing the NIP's concern about the report's scientific validity, and concern that it could threaten immunization rates and raise the risk of disease between scheduled immunizations. In fact, it may increase the autism that is of such concern, since MMR protects against the congenital rubella that is one cause of autism. Dr. Orenstein asked for sense of the ACIP members about the current policy.

Critique of Uhlmann et al Study. Dr. Bill Bellini reviewed the Uhlmann et al study on MMR and developmental disorders. The paper was written with some skill, using the same type of data presented to Rep. Burton's committee a few years ago on individuals with developmental disorder. However, its weaknesses include:

- The cases are inadequately described with respect to the type of developmental disorder(s); the reasons for biopsy were not clearly defined; the subjects' vaccination status was unclear, as was or whether the children had wild-type infection.
- The controls were selected among developmentally normal individuals, but some were diagnosed with Crohn's disease and ulcerative colitis. Previous publications have identified measles associated with diseases of the gut as well. It is unknown if individuals pre-screened as negative in prior experiments were now used as controls in the current study. The mean age is not provided (7 for cases, none for controls). If

they are older, this could affect the antigens found in the gut. There is no mention if the investigators or technicians being blinded to cases and controls, and no mention of possible contamination of specimens from collection through transport.

- Excellent molecular techniques were used: TaqMan Reverse Transcriptase-Polymerase chain reaction (real time RT-PCR), which is very sensitive and allows quantitation. When used with in-cell RT-PCR 9, it can preserve the morphology of the cell and surface markers to determine the presence of RNA and in what type of cell and what specific cell. Although real-time PCR of clinical specimens was done, it was not done with N gene primers, although N is the most abundant message. Finally, while they copied number calculations, they provided no data or standard curves to judge if the system was properly used, and only provided ranges (e.g., ability to detect from one copy to 300,000 copies). They showed their RNA band analyses, but these are not similar to examples of measles RNA analyses done in gel. Among other technical weaknesses were a puzzling switch to the use of nucleoprotein primers and inconsistent utilization of F, H, and N gene probes. Finally, the sequencing windows described are too small to differentiate between measles vaccine sequences and wild-type sequences. They would have been able to amplify the nuclear proteins if they had chosen to use them, but they did not.
- The study conclusions are a gross overstatement of the results, and the authors did not provide the opportunity to analyze their data.

Review of the Allegations in the U.K.
Dr. David Salisbury reported the need in the U.K. to continuously deal with this paper's allegations, including response to endless numbers of unique reports of children becoming autistic "overnight" after receiving MMR. The paper was leaked and published on the Internet, and received a great deal of media coverage. Other reviews were done and paralleled Dr. Bellini's comments. A number of methodological failures were raised, as well as design failures which prevented knowing which factor was the operant one leading to the conclusions reached.

After its release, Dr. Wakefield was challenged about the cases in the study, and admitted that not all had received MMR; some had received a single measles vaccine. This defeats the study's suggestion to replace MMR with a monovalent vaccine. As a result, the Chief Medical Officer wrote to Dr. Wakefield, asking how the controls could have Crohn's disease when two years earlier he had said this would be impossible since they would have measles virus in their intestines. Those answers are needed to confirm a serious concern about this vaccine. Independent review of his samples and raw data were also requested. Many have commented that no conclusions can be drawn from this work. The data needed are not there and the data present are not what is needed. As of noon on this day, Dr. Wakefield had not responded to those questions.

When Dr. Orenstein asked if the ACIP had any interest in altering its recommendation on MMR, laughter and thumbs down were the response.

Public comment was solicited, to no response. With the thanks of Dr. Modlin and Snider, the meeting adjourned at 2:19 p.m.

I hereby confirm that these Minutes are accurate to the best of my knowledge.

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John Modlin, M.D. , Chair

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Date